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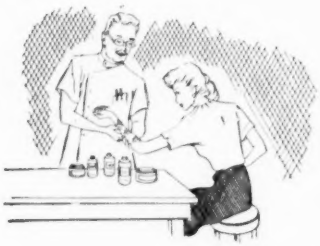

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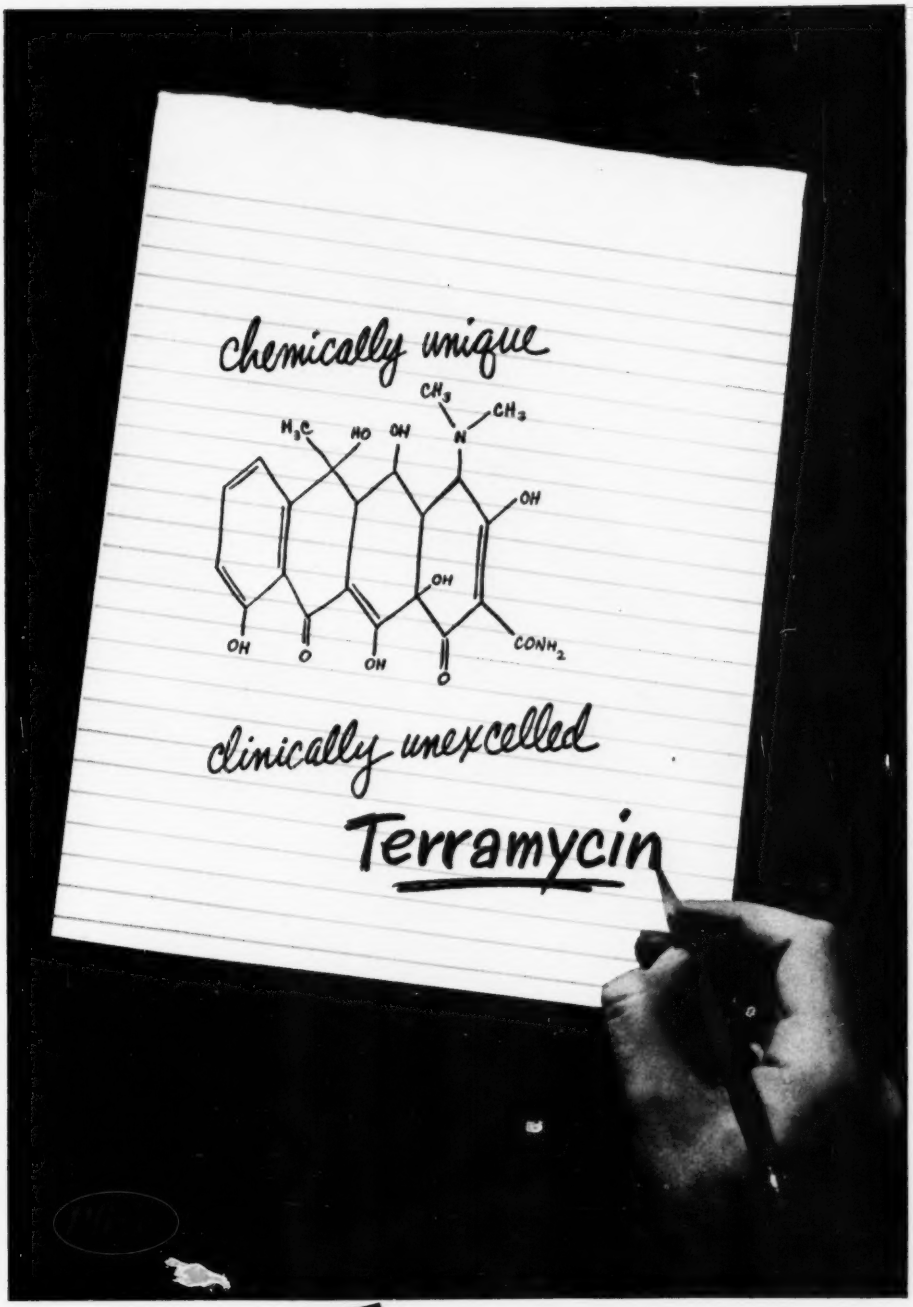

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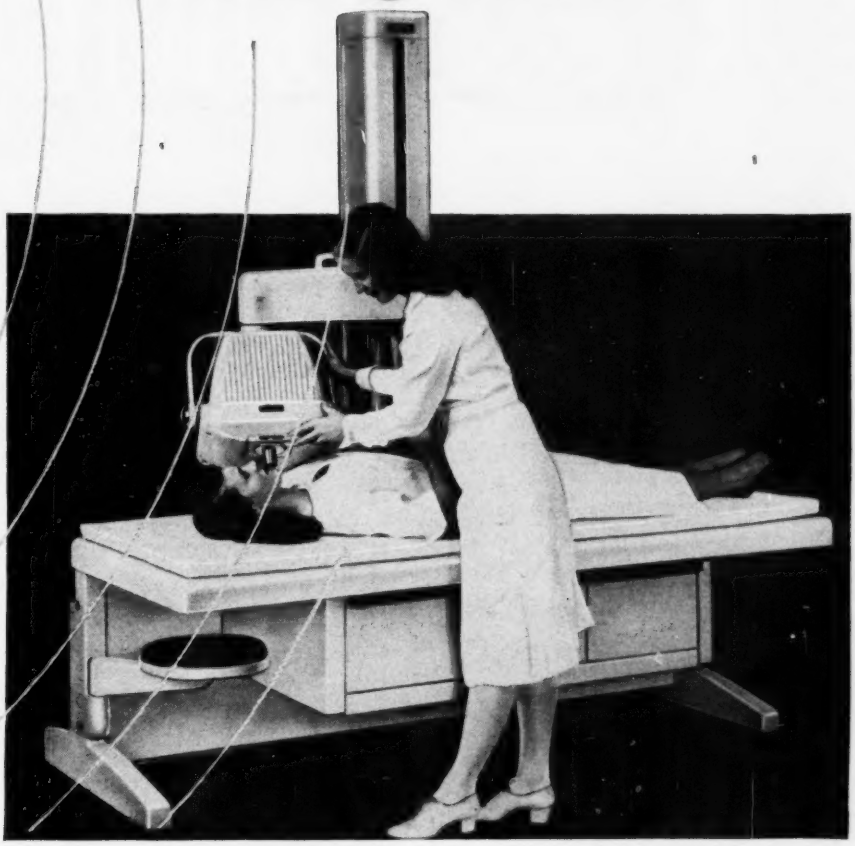

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1 Gross, Elmer R., M.D.; Wright, Carroll S., M.D.; Oral Bismuth Therapy in Syphilis and Various Dermatoses—Paper presented at the Pennsylvania Medical Society Meeting, October 8, 1946 at Philadelphia, Pennsylvania.

2 Gross, Elmer R., M.D.; Howles, James K., M.D.; Non-Specific Treatment of Dermatoses and Adjunctive Therapy of Syphilis with Oral Sodium Bismuth Triglycollamate. Read before the Section of Dermatology and Syphilology Meeting of the Centennial Meeting of the A.M.A. at Atlantic City, New Jersey, June 12, 1947.

3 Year Book of Dermatology and Syphilology, 1946, page 31.

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7 Miller, Thomas H., M.D. and Delaney, James R., M.D.; Oral Bismuth therapy in Dermatology. Archives of Dermatology and Syphilology, Vol. 60, August 1949.

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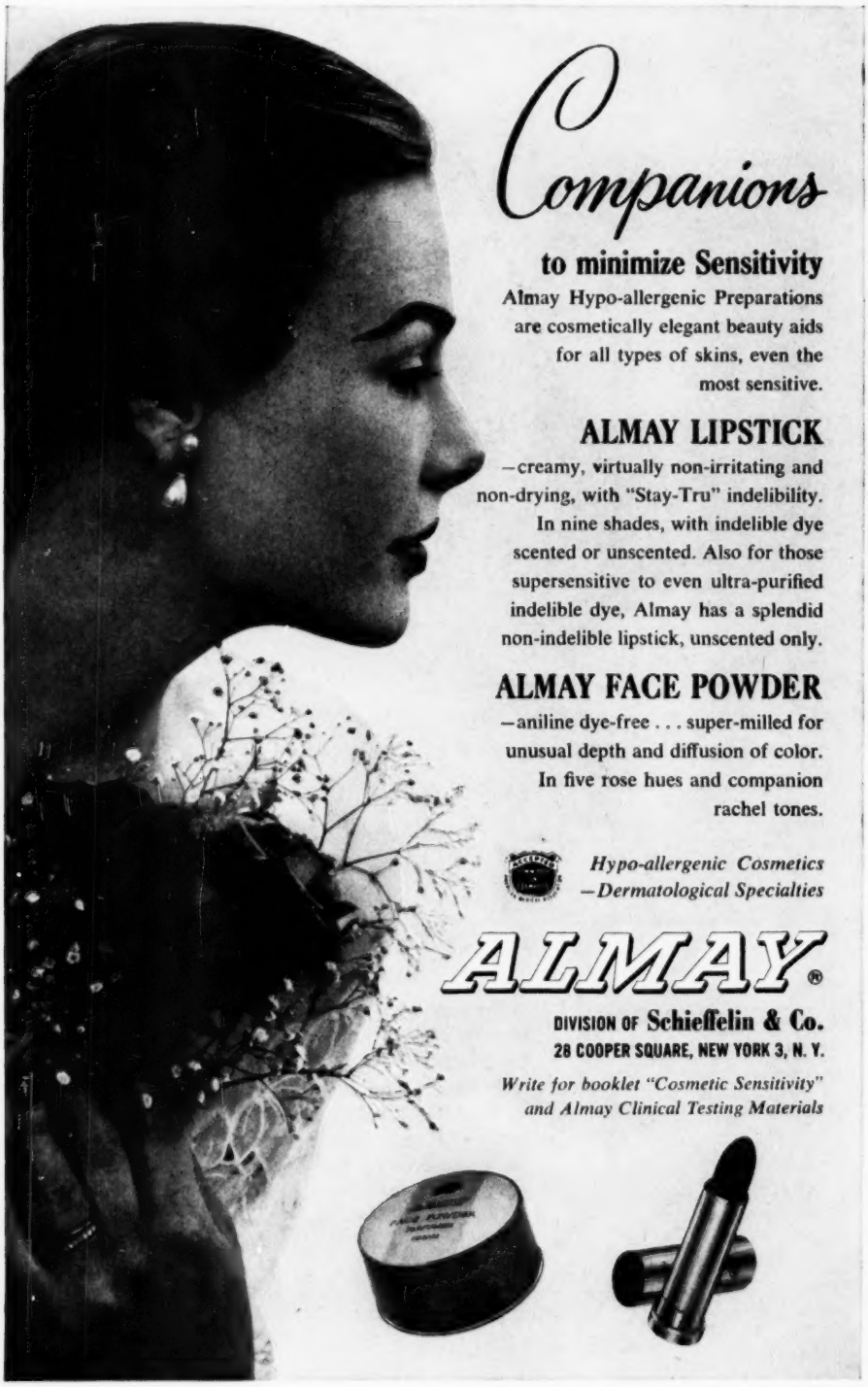

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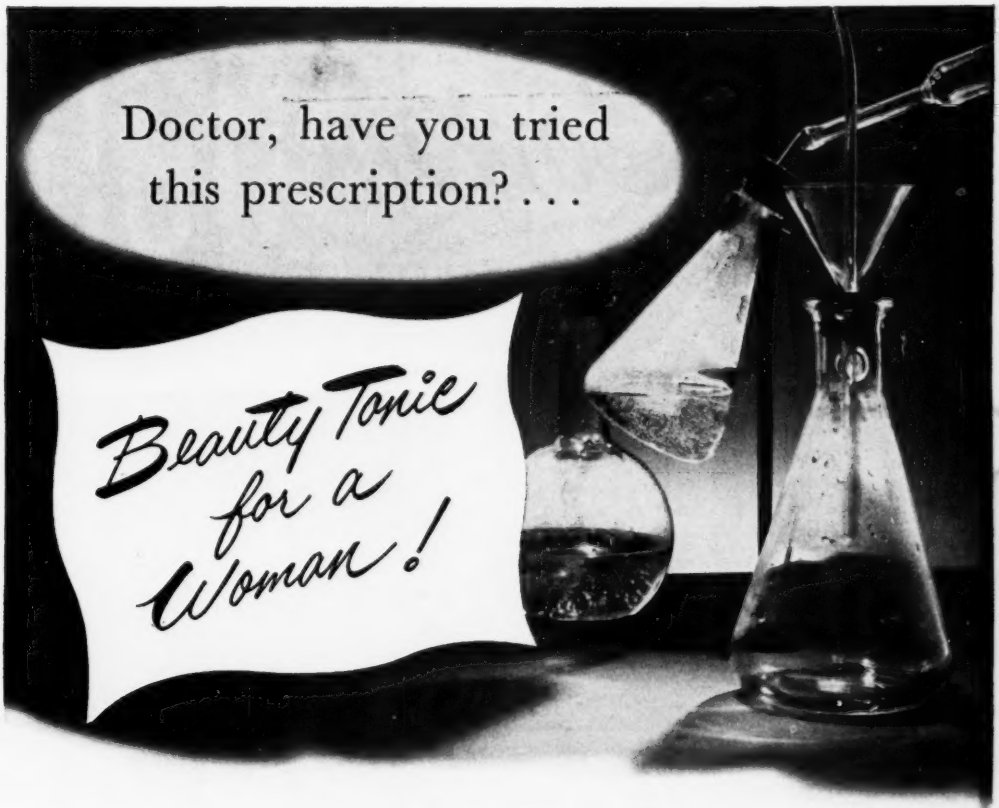

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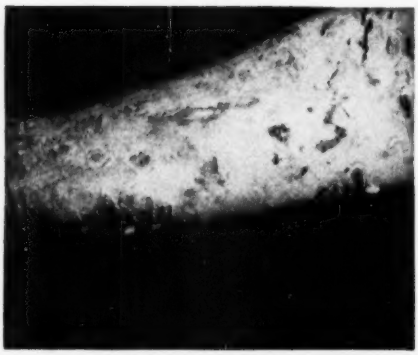

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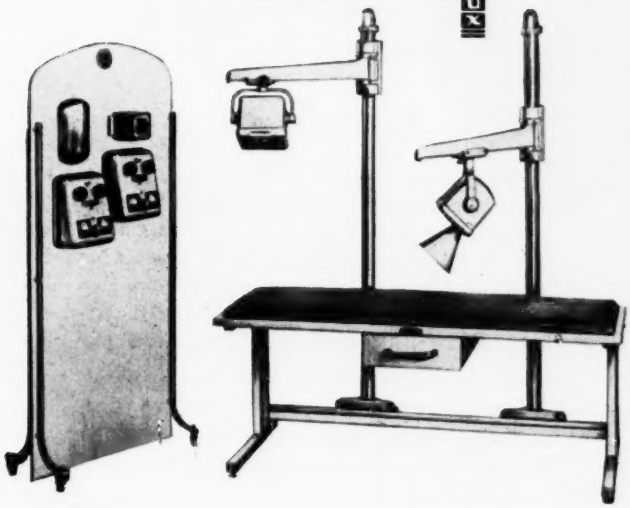

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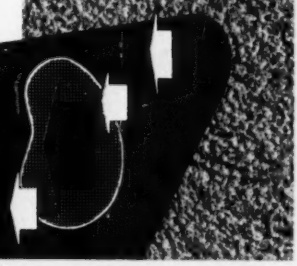

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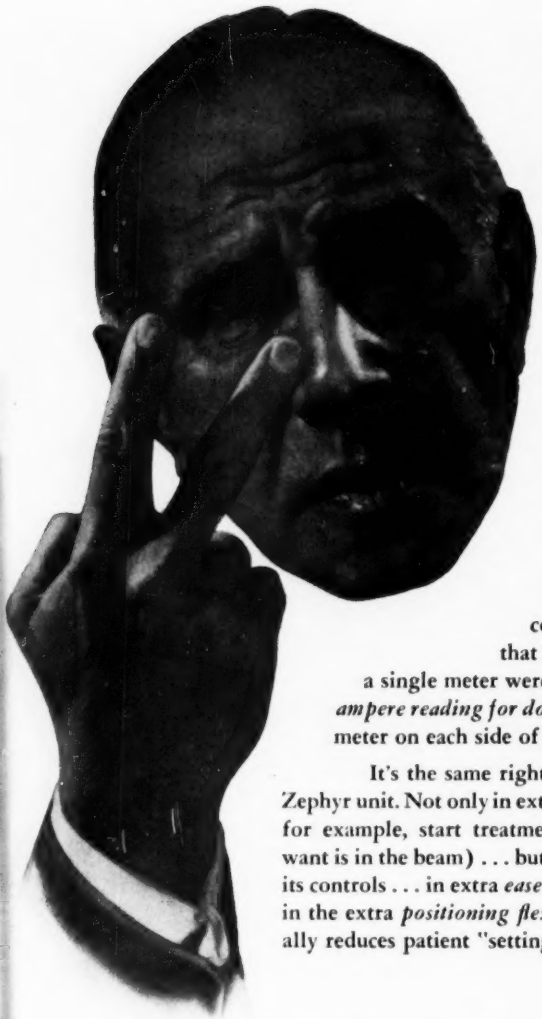

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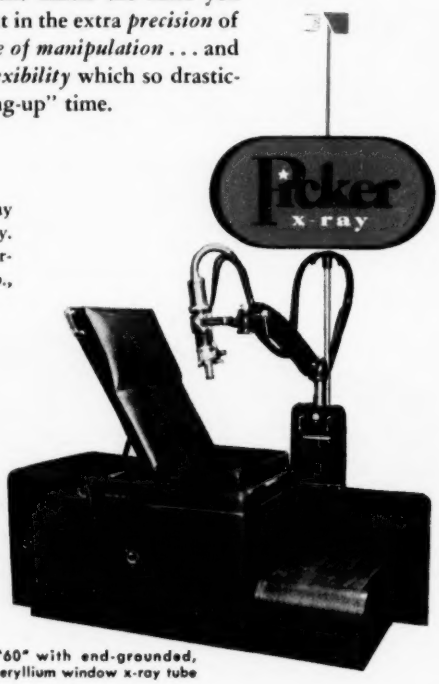

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ISOPHASIC REACTION FOLLOWING EXPERIMENTAL SUPERINFECTION OF LEISHMANIA TROPICA

A. DOSTROVSKY, M.D.
F. SAGHER, M.D.
AND
A. ZUCKERMAN, Ph.D.
JERUSALEM

THE DEVELOPMENT of immunity to superinfection with Oriental sore is delayed until parasites are no longer found in the primary lesion. In general, patients recovering from Oriental sore remain immune for life, after total cicatrization of the site of the primary infection. In a certain number of cases, however, relapse lesions may develop at the periphery of the primary scar, within the scar, or at some distant site. Thus, among 600 patients treated for Oriental sore at the Hadassah dermatological outpatient department in Jerusalem, approximately 10% were relapse patients.

The leishmanin test, an allergic skin reaction analogous to the tuberculin test, has proved to be a reliable indication of previous exposure to Leishmania tropica.[1] Sagher [2] has shown that the degree of sensitivity to leishmanin is greater in patients with leishmaniasis recidiva (relapsing cutaneous lesions) than in those with leishmaniasis nodosa (primary cutaneous lesions), since positive tests were still obtained in the relapse patients with dilutions no longer capable of eliciting reactions in patients with primary lesions.

The mechanisms for the development of the allergic leishmanin reaction and of immunity to L. tropica are apparently not identical since hypersensitivity, which

From the Department of Dermatology and Venereology (Dr. A. Dostrovsky, Director) and the Department of Parasitology (Dr. S. Adler, Director), Hebrew University-Hadassah Medical School.

1. (*a*) Wagener, E. H.: A Skin Reaction to Extracts of Leishmania Tropica and Leishmania Infantum, Berkeley, Calif., University of California Press, 1923, Univ. California Publ. Zool. **20**:477-488, 1923. (*b*) Jessner, M., and Amster, S.: Leishmania Vaccine Reaction, Deutsche med. Wchnschr. **51**:784-785 (May 8) 1925. (*c*) Jessner, M.: Untersuchungen über die Wirkung von Leishmaniavaccine bei experimenteller Hautleishmaniose, Arch. Dermat. u. Syph. **153**:237-247, 1927. (*d*) Montenegro, J.: Cutaneous Reaction in Leishmaniasis, Arch. Dermat. & Syph. **13**:187-194 (Feb.) 1926. (*e*) Dostrovsky, A.: The Diagnostic Value of Leishmania Vaccine, Ann. Trop. Med. **29**:123-128 (July 17) 1935. (*f*) Dostrovsky, A., and Sagher, F.: The Intracutaneous Test in Cutaneous Leishmaniasis, ibid. **40**:265-269 (Dec.) 1946.

2. Sagher, F.: Activation of an Originally Negative Intracutaneous Leishmania Vaccine Reaction, Acta med. orient. **5**:82-85 (March) 1946; The Response of Scars of Cutaneous Leishmaniasis to the Injection of Leishmania Tropica Vaccine, Brit. J. Dermat. **59**:205-213 (June) 1947; Leishmania Vaccine Test in Leishmaniasis of the Skin (Oriental Sore): Quantitative Experiments, Arch. Dermat. & Syph. **55**:658-663 (May) 1947.

develops within a few days of inoculation and remains high for the remainder of the patient's life, is not accompanied by immunity during the initial phase of the lesion, when parasites abound.[3] The fact that relapse patients are more leishmanin-sensitive than patients with primary lesions while they have obviously not been able to develop an efficient suppressive mechanism further supports the separate natures of the allergic and the immune mechanism.

The present study was undertaken to determine whether patients with leishmaniasis recidiva were immune to superinfection with viable L. tropica parasites and, in case they were susceptible, whether the clinical reaction form resembled the early (nodosa) or the late (recidiva) type.

MATERIALS AND METHODS

Six patients with relapsing cutaneous leishmaniasis were the object of our study. Five of them came from Iraq within the 16 months previous to the experiments, and one from Afghanistan 11 years previously.

Clinical diagnosis of their condition was confirmed by strongly positive leishmanin tests in all cases, and by culture of L. tropica from the periphery of the relapse lesions in five of the six cases. Repeated attempts to culture parasites from the lesion of the sixth patient were unsuccessful, owing perhaps to ulceration and bacterial contamination of the lesion, which extended over the mucosal surface of the upper lip.

The relapsing lesion of each patient was treated as follows:

1. Leishmaniasis recidiva was first diagnosed on clinical grounds.

2. Tissue juice was aspirated for culture from a peripheral area in which the lesion was apparently in an active state, i. e., in which apple-jelly nodules were observable under diascopic pressure. The area to be cultured was disinfected with iodine, washed with 70% alcohol, permitted to dry, and lanced. Material was withdrawn from the depth of the incision with a very fine capillary pipette, and was immediately transferred to the culture medium, which consisted of semisolid Locke-agar + 10% fresh, defibrinated rabbit blood, as described by Adler and Theodor.[4] Ten units of penicillin per milliliter of medium was added as a safeguard against contamination. Several drops of tissue juice were introduced into each of several tubes.

3. Films prepared from a drop of tissue juice were dry-fixed in methyl alcohol absolute and stained with Giemsa's stain. At least 100 oil immersion fields of such a film were examined before a negative microscopic diagnosis was made.

4. Biopsy specimens to determine the histological nature of the lesion were taken from a region similar to that in treatment 2 above. Tissue samples fixed in Zenker's solution were cut at 8 to 10 μ and stained with hematoxylin and eosin stain.

Wassermann, Kahn, and tuberculin tests done before further treatment of the patients were negative in all six cases.

The strain of L. tropica employed in superinfecting the patients was an Iraqi strain isolated three months prior to the superinfection experiments from the relapse lesion of one (Y. S.) of the six patients studied. It has since proved to be infective in patients not previously exposed to L. tropica and produced in them a lesion essentially indistinguishable from leishmaniasis nodosa. The strain has been maintained by serial passage in the agar-Locke-rabbit serum medium mentioned above. Leptomonads to be injected were grown in a liquid medium of the following composition (in order to avoid inoculating agar or foreign red cells): nutrient bouillon contain-

3. (*a*) Dostrovsky, A.: The Incubation Period in Experimental Cutaneous Leishmaniasis, Acta med. orient. **4**:303-305 (Sept.) 1945; (*b*) The Leishmania Test in Experimental Leishmaniasis (Oriental Sore) in Human Subjects, J. Invest. Dermat. **10**:435-439 (June) 1948. (*c*) Adler, S., and Zuckerman, A.: Observations on a Strain of L. Tropica After Prolonged Cultivation: Notes on Infectivity and Immunity, Ann. Trop. Med. **42**:178-183 (Sept.) 1948.

4. Adler, S., and Theodor, O.: The Identity of Leishmania Tropica Wright, 1903, and Herpetomonas Papatasii Adler, 1925, Ann. Trop. Med. **20**:355-364 (Dec. 17) 1926.

ing 0.1% glucose and 10% rabbit serum. Rich cultures, generally one to two weeks old, were washed free of medium and metabolites by being suspended in a relatively large volume of sterile saline; they were then centrifuged and the supernatant fluid discarded. The entire procedure was repeated twice. The deposit of washed, living leptomonads was then diluted with sufficient saline to yield a suspension containing 1,000,000 or 10,000,000 parsites in 0.1 ml. of fluid, as estimated with the aid of a Thoma counting chamber.

In superinfecting, either 1,000,000 or 10,000,000 viable culture leptomonads were inoculated intradermally over the deltoid muscle of the arm. We were interested in injecting more leptomonads than are generally introduced by the bite of a Phlebotomus, since numerous instances are on record of such an inoculum being inadequate to establish infection. It has been estimated by Adler (personal communication cited in Dostrovsky [3a,b]) that as many as 2,000 parasites may be introduced by a sandfly when biting. Fifty-six thousand parasites were found to give rise to no perceptible lesion in one of our patients, and 1,000,000 leptomonads were used as the minimal inoculum thereafter.

TABLE 1.—*Clinical and Laboratory Data on Six Patients with Leishmaniasis Recidiva*

			Relapsing Lesion					
Patient	Age, Yr.	Sex	Clinical Picture	Duration (Yr.)	L. D.* Bodies in Tissue Smears	Parasites Obtained in Culture	Histological Nature of Lesion	Intradermal Leishmanin Test
A. S.	26	M	L. r.† on nose	13	—	+	Tuberculoid granulation tissue	+
Y. S.	18	M	L. r. on nose and cheeks	15	—	+	Tuberculoid granulation tissue	+
S. C.	12	F	L. r. on left thigh	ca. 10	—	+	Tuberculoid granulation tissue	+
Z. M.	12	M	L. r. on left cheek and forehead	ca. 10	—	+	Tuberculoid granulation tissue	+
F. M.	13	M	L. r. on left cheek, lips and mandibular region	6	—	—	Tuberculoid granulation tissue	+
D. C.	14	F	L. r. on left cheek	13.8	—	+	Tuberculoid granulation tissue	+

* L. D. = Leishmania donovani.
† Leishmaniasis recidiva.

The lesions developing at the site of superinfection were studied by the same methods as those described for the relapse lesions (clinically, histologically, by culture, and by microscopic examination of tissue juice) for from 6 to 18 months following inoculation.

EXPERIMENTAL STUDIES

The clinical and experimental data on the six patients studied are presented in Tables 1 and 2. It is noteworthy that microscopic evidence of the presence of parasites at the sites of relapse or superinfection was never recorded and that, even when positive results were obtained by culture of the superinfection sites, not all the inoculated tubes always contained parasites. Judging from both of these facts, the number of parasites at the superinfection sites must have been low as in typical recidiva lesions, and not high, as in typical nodosa lesions.

Clinical Course of the Experimental Superinfection.—The clinical courses of the experimental superinfections induced by a standard inoculum were similar, and the following general description is based on events succeeding the inoculation of 1,000,000 leptomonads over the left deltoid muscle of four patients.

TABLE 2.—*Experimental Data on the Superinfection of Leishmania Tropica in Six Patients with Leishmaniasis Recidiva*

	First Superinfection: One Million Leptomonads Intradermally in Left Deltoid Region							Second Superinfection: Ten Million Leptomonads Intradermally in Right Deltoid Region						
Patient	Days Between Inoculation and Culture	L. D.* Bodies in Tissue Smears from Inoculation Site	Result of Culture	Clinical Appearance of Inoculation Site	Histological Structure of Inoculation Site	Months Under Observation	Lesion at End of Observation Period	Days Between Inoculation and Culture	L. D.* Bodies in Tissue Smears from Inoculation Site	Result of Culture	Clinical Appearance of Inoculation Site	Histological Structure of Inoculation Site	Months Under Observation	Lesion at End of Observation Period
A. S.†	236	—	—	Local reaction disappearing in 6 weeks	.....	18	No signs	...	..	..	L. r.*	108th day tuberculoid; 200th day tuberculoid	17	L. r.
Y. S.	9	—	—	L. r.	9th day acute inflammation; 77th day granuloma with epithelioid cells	13	Scar	21	—	—	.....	.....	..	.....
	77	—	—	.....		..	.....	...	..	..	.....	.....	..	.....
	104	—	—	.....		..	.....	...	..	..	.....	.....	..	.....
	142	—	—	.....		..	.....	...	..	..	.....	.....	..	.....
	318	—	—	.....		..	.....	...	..	..	.....	.....	..	.....
S. C.	9	—	—	L. r.	.....	11	L. r.	17	—	—	L. r.	.....	10	L. r.
	33	—	—	.....	.....	..	.....	42	—	—	.....	.....	..	.....
	47	—	—	.....	.....	..	.....	74	—	+	.....	.....	..	.....
	72	—	—	.....	.....	..	.....	299	—	—	.....	.....	..	.....
	104	—	+	.....	.....	..	.....	...	..	..	.....	.....	..	.....
	329	—	—	.....	.....	..	.....	...	..	..	.....	.....	..	.....
Z. M.	9	—	—	L. r.	37th day tuberculoid	13	L. r.	17	—	—	L. r.	.....	12	L. r.
	33	—	—	.....		..	.....	74	—	+	.....	.....	..	.....
	47	—	—	.....		..	.....	286	—	—	.....	.....	..	.....
	104	—	+	.....	.....	..	.....	...	..	..	.....	.....	..	.....
	316	—	—	.....	.....	..	.....	...	..	..	.....	.....	..	.....
F. M.	17	—	—	Local reaction disappearing in 6 weeks	328th day scar tissue	10	No signs	27	—	—	Deep papule	.....	6	Ulcer
	34	—	—			..	.....	54	—	+		.....	..	.....
D. C.	9	—	—	L. r.	66th day tuberculoid	13	Scar	...	..	..	.....	.....	..	.....
	16	—	—	.....		..	.....	...	..	..	.....	.....	..	.....
	104	—	+	.....		..	.....	...	..	..	.....	.....	..	.....
	316	—	—	.....	.....	..	.....	...	..	..	.....	.....	..	.....

* L. r. = leishmaniasis recidiva.
L. D. = Leishmania donovani.
† Patient A. S. received 56,000 instead of 1 million parasites in the left deltoid region.

1. Forty-eight hours: A central papule is surrounded by an area of erythema, as in the leishmanin test. However, whereas this characteristic reaction disappears within a week in the leishmanin test, it persisted for 10 days at the superinfection sites.

2. Fourteen days: The erythema has disappeared but the papule persists.

3. Less than a month: The papule is practically gone. Scaling is observed at the superinfection site.

4. More than a month: The papule is re-formed, with a central crust, which is sloughed off a few weeks later. The papule persists, and now has a diameter of about 0.5 cm.

Fig. 1.—About two months after inoculation with 1,000,000 flagellates of Leishmania tropica. The lesion is bluish-red, infiltrated, and covered with a central crust.

5. Six weeks: A reddish-yellow area of infiltration develops at the inoculation site. Under diascopic pressure, tiny, yellowish apple-jelly nodules are seen.

6. Six months: In all four patients, the area of infiltration has gradually spread, reaching a maximum diameter of 0.75 cm. The lesion remained at this stage until at least 11 months following inoculation. The clinical picture was now identical with that of leishmaniasis recidiva, as seen in the relapse lesions of the same patients.

7. Thirteen months: Spontaneous cure with cicatrization was observed in two cases. Residual peripheral infiltration persisted in two cases.

Fig. 2.—About four months after inoculation of 10,000,000 flagellates of L. tropica. The lesion is yellowish-brown and infiltrated. Apple-jelly nodules can be seen under diascopic pressure.

Fig. 3.—Between 6 to 10 months after inoculation a central scar is developing, surrounded by a yellowish-brown infiltrate.

Ten million leptomonads were inoculated intradermally over the right deltoid muscle of five of the six patients studied.[5] The course of events was similar to that following the inoculation of 1,000,000 parasites, but the reaction was more intense. The lesions at the site of inoculation of 10,000,000 parasites were all larger than those seen concurrently at the site of inoculation of 1,000,000 parasites (with a diameter of about 1 cm. as compared with 0.5 to 0.75 cm.), although the larger inocula were all administered one to five months after the injection of the smaller inocula.

Clinical and histological evidence of the similarity of the body's response in the relapse lesion and in the superinfection lesion is presented in Figures 1 to 6. Both relapse and superinfection lesions developed very slowly, healing at their centers

Fig. 4.—Site of inoculation of 10,000,000 flagellates 18 months after inoculation. Apple-jelly nodules may still be seen on diascopic pressure at this time.

while spreading peripherally. Both lesions ranged in color from brownish-yellow to brownish-red, and in both cases apple-jelly tubercles could be demonstrated on diascopic pressure. Both relapse and superinfection lesions were flat and only slightly elevated, covered with scales, nonulcerating and indolent, and tending to become circular, with a narrow peripheral band of tubercles surrounding an atrophic scar.

5. One patient reacted rather violently to the inoculation of 10,000,000 flagellates, with regional adenitis, generalized malaise, nausea, sweating, pallor—in short, with a condition reminiscent of anaphylactic shock. This reaction occurred five months after an inoculation of 1,000,000 parasites, and it may have been associated with the possible presence of traces of rabbit serum in the inoculum.

This clinical picture may be contrasted with the typical early lesion of leishmaniasis nodosa, which is conically elevated, often with a central crust under which ulceration can be seen, is bluish-red, with indistinct borders, and does not show applejelly nodules under pressure with the diascope.

A total of seven biopsies were performed on five patients, the earliest 9 days and the latest 328 days after inoculation. In four biopsy specimens from three patients tuberculoid granulation tissue was observed; and in one case epithelioid cells without typical tuberculoid arrangement were seen. The earliest observation of tuberculoid tissue was 37 days following inoculation, and the latest was at 200 days. An acute inflammatory process was found in a specimen taken 9 days after inoculation, and scar tissue was found at the cured superinfection site in one specimen taken 328 days after inoculation.

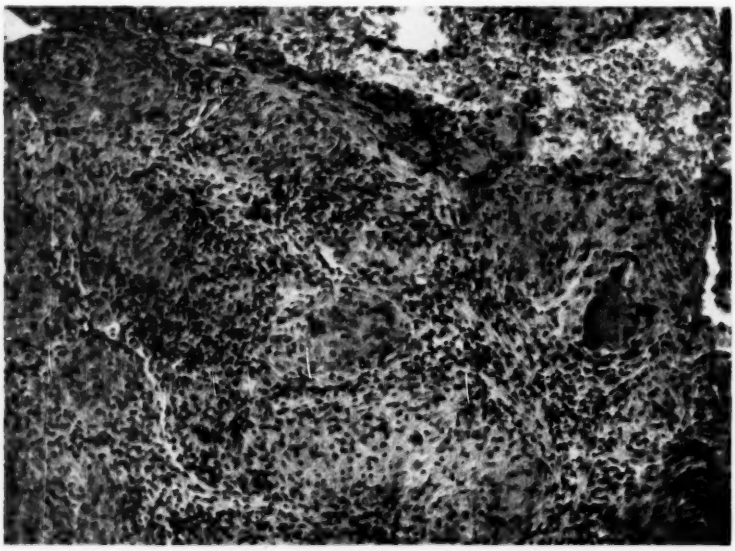

Fig. 5.—Section from a naturally occurring relapse lesion on the nose showing tuberculoid granulation tissue; × 145.

Attempt to Demonstrate Antibodies Against L. Tropica in the Serum of Patients with Leishmaniasis Recidiva.—When our relapse patients were observed to be susceptible to superinfection with L. tropica, it was considered of interest to investigate other possible evidences of immunity—for example, to determine whether circulating antibodies against this parasite might perhaps be demonstrated by culturing homologous parasites in the presence of serum suspected of containing antibodies. Noguchi [6] has shown that rabbits immunized by a series of intravenous injections of cultures of L. tropica yield serum which when incorporated in agar-Locke med-

6. Noguchi, H.: Action of Certain Biological, Chemical, and Physical Agents upon Cultures of Leishmania: Some Observations on Plant and Insect Herpetomonads, Proceedings of the International Conference on Health Problems in Tropical America, Boston, United Fruit Company, 1925, pp. 455-479.

ium supports a different type of growth from that observed in medium prepared with normal rabbit serum. Instead of the growth being confined to the upper 3 or 4 mm. of the medium, as in normal serum, parasites grown in homologous immune serum tended to penetrate diffusely much more deeply into the tube. Furthermore they grew in clumps and not discretely as in normal serum. And finally, many Leishmania donovani bodies were observed by Adler and Theodor [4] to develop in immune serum, whereas leptomonads are the form found exclusively in normal serum.

Reasoning that if antibody against L. tropica were present in the blood of our patients with leishmaniasis recidiva, their serum might be expected to induce similar changes in homologous parasites grown in their presence, we incorporated samples of the serum of each of the six patients in place of rabbit serum in such cultures.

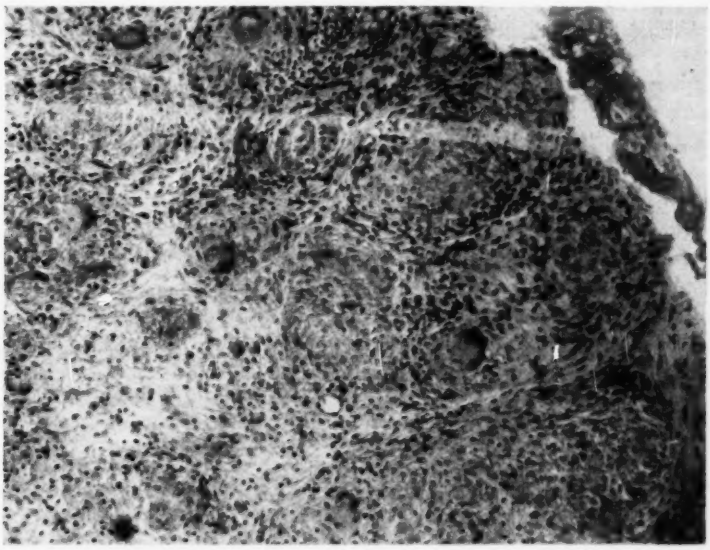

Fig. 6.—Experimental superinfection with L. tropica in the same patient as in Figure 5 also showing tuberculoid granulation tissue; × 145.

None of the cultures grown in our patients' serums differed in any appreciable way from controls prepared with normal rabbit or normal human serum.

Circulating antibody against L. tropica was therefore not demonstrated in the blood of patients with leishmaniasis recidiva.

COMMENT

Experimental superinfection in early cutaneous leishmaniasis nodosa was attempted by Berberian,[7] who gave a series of three inoculations, each consisting of 500,000 parasites, to each of five volunteers. Positive superinfections were obtained as long as parasites were to be found in smears of the primary lesion, but superin-

7. Berberian, D. A.: Cutaneous Leishmaniasis (Oriental Sore): I. Time Required for Development of Immunity After Vaccination, Arch. Dermat. & Syph. **49**:433-435 (June) 1944.

fection failed when parasites were no longer detectable in the primary lesion, indicating that immunity to superinfection had developed by this time. Katzenellenbogen [8] observed a violent local reaction after the inoculation of 1,500,000 parasites in a patient with leishmaniasis recidiva.

Five of our six patients with relapsing leishmaniasis failed to develop an efficient defense against superinfection, since we succeeded in reinfecting them with viable L. tropica grown in vitro. Indeed, it is quite possible that superinfection occurred in the sixth patient, A. S., as well, although we failed to demonstrate it on the single occasion when we attempted to culture material from his infection site. He may actually have been on the way to recovery following transitory infection, such as that observed in other patients from whom a series of cultures rather than a single culture were available. It is clear from inspection of Table 2 that any of the five other patients shown to have been susceptible to superinfection might have been recorded as refractory if their inoculation sites had been cultured only once rather than repeatedly.

We have shown in an additional series of patients not formerly exposed to leishmania that our strain is capable of eliciting typical nodosa-type lesions. It may therefore be concluded that the production of recidiva—rather than nodosa—type lesions in our patients is due to the host, and not to characters peculiar to the parasite strain.

We consider that the fact that cultures from several of our patients were negative for several months after superinfection and became positive only subsequently indicates multiplication of the surviving parasites in the superinfection lesion following the initial destruction of the overwhelming majority of the inoculated flagellates. Parasites were still not very abundant even when positive cultures were obtained, since not all tubes seeded at these times with tissue juice from the superinfection sites yielded positive cultures and since smears from these lesions were throughout microscopically negative.

In this respect, as well as histologically and clinically, the superinfection lesions resembled typical relapse lesions, in which parasites are notoriously difficult to demonstrate microscopically, in contrast to primary lesions, in which L. D. bodies are generally very numerous.

The histological course of development of the superinfection lesions as well as of the relapse lesions is in accord with the law of Jadassohn and Lewandowsky,[9] which holds that antigens disintegrating at localized sites induce tuberculoid reactions whereas those circulating throughout the body induce nonspecific inflammatory reactions. Superinfection lesions were shown to have a tuberculoid structure similar to that of the relapse lesion even at an early date, during the phase clinically resembling leishmaniasis nodosa, and the tuberculoid nature of the lesion persisted until cicatrization. Thus, superinfection of L. tropica in patients with leishmaniasis recidiva induced lesions similar throughout in their histology to those of leishmani-

8. Katzenellenbogen, I.: Vaccination Against Oriental Sore: Report of Results of 555 Inoculations, Arch. Dermat. & Syph. **50**:239-242 (Oct.) 1944.

9. Lewandowsky, F.: Die Tuberkulose der Haut, in Langstein, L.; von Noorden, C.; von Pirquet, C., and Schittenhelm, A.: Enzyklopædie der klinischen Medizin, Berlin, Julius Springer, 1916, pp. 1-330.

asis recidiva. Clinically an accelerated nodular phase was rapidly superseded by a lesion of the recidiva type, followed by cure and scarring in several cases under observation for more than a year.

All of our lines of evidence, based on clinical, microscopic, histological, and culture findings, thus support the view that the inoculation of viable flagellates of L. tropica into patients with leishmaniasis recidiva induced superinfection lesions closely resembling recidiva-type and not nodosa-type lesions. We suggest the designation of this phenomenon as an isophasic reaction.

Our results with superinfection in cases of leishmaniasis recidiva leading to an isophasic reaction recall those of Finger, Landsteiner, and others [10] working with superinfection of active syphilis in guinea pigs, apes, and man during early and late stages of the infection. They showed that during the period of florid infection no absolute immunity to superinfection can be demonstrated but that either homologous or foreign strains regularly induce pathological responses corresponding to the phase of the disease in the recipient host at the time of superinfection.

SUMMARY AND CONCLUSIONS

Successful superinfection of Leishmania tropica in patients with relapsing cutaneous leishmaniasis has been obtained. Eight out of 10 superinfections with 10,000,000 induced them following four out of five superinfections. One superincutaneous leishmaniasis recidiva yielded positive leishmanial lesions. One million parasites induced such positive lesions following four out of five superinfections, and 1,000,000 or 10,000,000 culture leptomonads of L. tropica in five patients with fection, in a sixth patient, was unsuccessful.

After two to six months all the superinfection sites were clinically and histologically similar to lesions of leishmaniasis recidiva. Histologically the lesion was tuberculoid in structure. The organism of a patient with leishmaniasis recidiva thus consistently reacted to the reintroduction of L. tropica by the formation of the relapsing type of leishmanial lesion (isophasic reaction).

This isophasic reaction was shown to be associated with factors in the host and not in the parasite.

Whereas the intradermal reaction to leishmanin was strongly positive in all patients, immunity was insufficient to prevent superinfection. This is interpreted as supporting the view that the development of allergy and immunity against L. tropica are separate processes.

No circulating antibody against L. tropica was demonstrated in the serums of six patients with leishmaniasis recidiva when parasites were grown in a medium incorporating such serums.

10. Finger, E.: Die allgemeine Pathologie der Syphilis, in Finger, E.; Jadassohn, J.; Ehrmann, S., and Gross, S.: Handbuch der Geschlechtskrankheiten, Vienna and Leipzig, Alfred Hölder, 1912, Vol. 2, pp. 896-958.

USE OF TWO STILBENE DERIVATIVES (DIETHYLSTILBESTROL AND STILBAMIDINE) IN TREATMENT OF BLASTOMYCOSIS

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SYSTEMIC blastomycosis usually is fatal. In a review of the literature Martin and Smith [1] noted a mortality of 92% in patients who had been followed for two years or longer. Cutaneous blastomycosis rarely causes death, but untreated lesions may be present for many years.

Since the synthesis of a group of compounds known as aromatic diamidines by Ashley and his co-workers [2] in the course of their studies on trypanocidal drugs, a surprisingly large number of other therapeutic effects have been shown both in vitro and in vivo. The first hint that the aromatic diamidines might be fungistatic came from the studies of Elson [3] who used one member of this group, "propamidine" (4,4'-diamidinodiphenyloxypropane hydrochloride) in several in vitro experiments with some of the organisms responsible for the superficial and deep mycoses. The experiments with Blastomyces dermatitidis showed effective fungistatic properties in dilutions as low as 0.075 mg. of "propamidine" for each 20 cc. of agar. This result was exceeded only by the fungistatic effect of the drug on Sporotrichum schenckii.

Stilbamidine (4,4'-stilbenedicarboxyamidine), also an aromatic diamidine, has been studied extensively, so far as its effect on trypanosomes, protozoa, and bacteria is concerned,[4] but no in vitro work has been done on its effect on fungi. Colbert and associates [5] reported on the use of "propamidine" in the treatment of cutaneous

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1. Martin, D. S., and Smith, D. T.: Blastomycosis (American Blastomycosis, Gilchrist's Disease): I. Review of the Literature, Am. Rev. Tuberc. **39**:275-304, 1939; II. Report of 13 New Cases, ibid. **39**:488-515, 1939.

2. Ashley, J. N.; Barber, H. J.; Ewins, A. J.; Newberry, G., and Self, A. D.: A Chemotherapeutic Comparison of the Trypanocidal Action of Some Aromatic Diamidines, J. Chem. Soc. 103-116, 1942.

3. Elson, W. O.: The Antibacterial and Fungistatic Properties of Propamidine, J. Infect. Dis. **76**:193-197, 1945.

4. Schoenbach, E. B., and Greenspan, E. M.: The Pharmacology, Mode of Action and Therapeutic Potentialities of Stilbamidine, Pentamidine, Propamidine and Other Aromatic Diamidines: A Review, Medicine **27**:327-377, 1948.

5. Colbert, J. W., Jr.; Strauss, M. J., and Green, R. H.: Treatment of Cutaneous Blastomycosis with Propamidine: Preliminary Report, J. Invest. Dermat. **14**:71-73, 1950.

blastomycosis, and Schoenbach and his co-workers [6] used the combination of "propamidine" and stilbamidine in the treatment of two patients with systemic blastomycosis. These encouraging preliminary reports and the in vitro effects of "propamidine" led to our in vitro study and clinical use of stilbamidine in treatment of both cutaneous and systemic blastomycosis.

The chemical similarity of the aromatic diamidines to diethylstilbestrol suggested the possibility that diethylstilbestrol might also have an effect on blastomycosis.

The fungistatic effect of diethylstilbestrol and stilbamidine compared with that of other sex hormones in cultures of B. dermatitidis is here reported in brief. Two patients with cutaneous blastomycosis treated with diethylstilbestrol and two patients with systemic blastomycosis treated with stilbamidine are reported on in detail.

TABLE 1.—*Fungistatic Action of Stilbamidine and Other Related Compounds on B. Dermatitidis**

Test Material	Medium	Temperature, C.	Growth at Specified Dilutions, Mg./Ml. 1	0.1	0.01	0.001	0.0001	0.00001	Control
Methyltestosterone	Sabouraud's	Room	.....	+	+	±	+	.....	.....
	Nutrient	37	.....	+	++	++	+	.....	.....
Testosterone	Sabouraud's	Room	.....	++++	++	+++	+++	.....	.....
	Nutrient	37	.....	++++	++	++	++	.....	.....
Cortisone	Sabouraud's	Room	++	+	+++	+	.....	.....	.....
	Nutrient	37	++	+	+	++	.....	.....	.....
Desoxycorticosterone	Sabouraud's	Room	.....	++	++	++	++	.....	.....
	Nutrient	37	.....	++	+++	++	++++	.....	.....
Progesterone	Sabouraud's	Room	.....	+	++	++	++++	.....	++++
	Nutrient	37	.....	++	++	++++	++++	.....	++++
Pregnenolone	Sabouraud's	Room	+++	+	+++	+	.....	.....	+++
	Nutrient	37	++	++	++++	++++	.....	.....	+++
Ethynyl estradiol	Sabouraud's	Room	.....	.....	+++	++	++	++	++
	Nutrient	37	.....	.....	+	++	+++	++	++
Estradiol	Sabouraud's	Room	.....	.....	+++	++	++	Contam	+
	Nutrient	37	.....	.....	++	++++	++++	++++	+
Diethylstilbestrol (tablets)	Sabouraud's	Room	.....	—	+++	+++	+++	.....	±
	Nutrient	37	.....	—	—	++	++	.....	±
Diethylstilbestrol (in oil)	Sabouraud's	Room	.....	+++	++	—	+	.....	—
	Nutrient	37	.....	—	—	—	—	.....	—
Stilbamidine	Sabouraud's	Room	—	—	—	±	.....	.....	.....
	Nutrient	37	—	—	—	±	.....	.....	.....
Plain control	Sabouraud's	Room	.....	.....	.....	.....	.....	.....	++++
	Nutrient	37	.....	.....	.....	.....	.....	.....	++++
Control with 0.5 ml. acetone added	Sabouraud's	Room	.....	.....	.....	.....	.....	.....	++
	Nutrient	37	.....	.....	.....	.....	.....	.....	++

* Explanation of symbols: ++++ indicates same growth as control; +++ indicates ¾ as much growth as control; ++ indicates ½ as much growth as control; + indicates ¼ as much growth as control; ± indicates suggestion of growth; — indicates no growth.

MYCOLOGICAL STUDY

Calculated amounts of the test materials listed in Table 1 were incorporated in Sabouraud's agar and nutrient agar so that serial dilutions of the test materials could be obtained. The slants were inoculated with measured quantities of the same suspension of B. dermatitidis. The cultures were then incubated, Sabouraud's at room temperature and nutrient agar at 37 C and the growth observed and recorded weekly. The solvent used for the test materials, except for stilbamidine, was acetone. Controls with added acetone were made, inoculated, and read. Stilbamidine, being soluble in water, was dissolved in water.

Stilbamidine showed definite fungistatic influence on B. dermatitidis, inhibition occurring at a level of 0.01 mg. per milliliter which is three times more concentrated than that obtained by Elson [3] (0.0037 mg. per milliliter with "propamidine").

6. Schoenbach, E. B.; Miller, J. M.; Ginsberg, M., and Long, P.: Systemic Blastomycosis Treated with Stilbamidine, J. A. M. A. **146**:1317-1318, 1951.

Diethylstilbestrol also showed promising inhibition. Of interest is the greater inhibition of diethylstilbestrol of the yeast form at 37 C. Methyltestosterone seems to be worthy of further investigation also. More extensive studies of the broader fungistatic potentialities of steroids, aromatic diamidines, and stilbenes will be reported elsewhere.

REPORT OF CASES

CASE 1.[7]—R. R. P., a white man, aged 72, was first seen in 1944 when he had the left external ear removed because of an extensive and recurrent squamous cell carcinoma. He did not return until September, 1950, when he was seen with a lesion on the bridge of his nose which extended laterally on each cheek and which had been present, as nearly as the patient could recall, since about 1947. With the onset of the lesion on the nose, a similar lesion appeared on the patient's upper lip.

Fig. 1 (Case 1).—*A*, beginning of resolution of blastomycosis of inner canthi, bridge of nose, and upper lip during diethylstilbestrol therapy. *B*, lesions healed four months later while patient was still taking diethylstilbestrol.

Examination showed a scaling, serpiginous lesion on the bridge of the nose which extended laterally on each cheek and caused an ectropion of the left lower lid. There were a few tiny abscesses at the border (Fig. 1*A*). Similar lesions were present on the upper lip. Microscopic examination of material from one of the abscesses showed budding organisms which were typical of B. dermatitidis.

During this period of hospitalization, the patient was found to have an inoperable carcinoma of the prostate, and administration of diethylstilbestrol, 1 mg. three times a day, was begun. He returned on several subsequent occasions, and on Nov. 24, 1950, it was noted that the lesions of blastomycosis had shown considerable improvement. On Jan. 4, 1951, the physician who saw the patient noted that there was no evidence of activity in any portion of the blastomycotic lesions and that scar tissue was replacing them. At that time (Jan. 4, 1951), because of the inactivity of the blastomycosis, no suitable material could be found for culture studies or

7. The reports on Cases 1 and 2 were provided by Dr. Edward P. Cawley, professor of dermatology, University of Virginia.

microscopic examination. The patient was still receiving the same dose of diethylstilbestrol (Fig. 1*B*). Again, on April 3, 1951, there was no evidence of activity in any part of the lesions. The patient was last seen on June 5, 1951, at which time all lesions had been replaced by scar tissue. The ectropion of the left lower lid persisted.

An x-ray examination of the chest on Sept. 9, 1950, showed pulmonary calcifications which the roentgenologist interpreted as an old healed tuberculosis. Further x-ray examinations showed no evidence of osseous metastases from the carcinoma of the prostate or blastomycosis of the lungs. Urinalysis gave normal results. The blood urea, on Sept. 9, 1950, was 46 mg. per 100 cc. A complete blood count was normal. A skin test with blastomycin done Sept. 8, 1950, showed an erythematous zone of induration 2 by 2 cm. in size at the end of 48 hours. The blood Kahn reaction was negative.

Fig. 2 (Case 2).—Large verrucous lesion on left midback.

CASE 2.—E. J., a white man, aged 68, was first seen in the University of Virginia Hospital in October, 1949, with the complaint of a lesion under his chin which had been present for approximately five months.

The patient stated that initially the lesion had the appearance of a "boil," but it had persisted and increased slightly in size until he was seen. The clinician noted under the left side of the chin a verrucous lesion which was typical, clinically, of blastomycosis, but the organism of B. dermatitidis was not seen in the material expressed from the lesion and no cultures were made. The patient refused treatment and went elsewhere to have the lesion excised.

He returned to the University of Virginia Hospital in June, 1950, having been apparently in good health in the interim. The operative site under the chin had healed satisfactorily. At the time of his return, the patient had another large verrucous lesion on the left upper back which was similar in appearance to the one previously present in the submental region but considerably larger. The lesion on the back was verrucous and serpiginous and had an actively growing border (Fig. 2). B. dermatitidis was not found on direct examination of the purulent

material expressed from the border of the lesion, and neither was it cultured. Biopsy however, revealed doubly contoured structures which were entirely compatible with those of B. dermatitidis.

During the course of his hospital study, he was found to have an inoperable carcinoma of the prostate, and diethylstilbestrol, 1.0 mg., was given three times a day. In the confusion that arose owing to the presence of two major diseases, the patient left the hospital without being advised of any treatment for his blastomycosis. Laboratory studies done at this time, including an x-ray examination of the chest, gave normal results.

The patient returned to the hospital in August, 1950, for a check of the carcinoma of his prostate. The lesion on the back had shown remarkable improvement. The patient was still taking diethylstilbestrol. He returned again in November, 1950, at which time the lesion on the back had been replaced by a superficial atrophic scar. The same dosage of diethylstilbestrol had been continued all this time. No new lesions of blastomycosis occurred. It was felt that diethylstilbestrol had definitely influenced the course of his patient's blastomycosis.

Case 3.—A. W., a Negro automobile worker, aged 38, was first seen at the University Hospital on Sept. 5, 1951. In July, 1949, while at work he was cut on the inner surface of the

Fig. 3 (Case 3).—Right wrist before stilbamidine treatment. Similar lesions were present on back and on right ankle. Patient also had pulmonary and lymph node blastomycosis.

lower right forearm. The area healed, but after a second similar cut several months later a small nodule formed at the site of trauma. The nodule suppurated and gradually enlarged into a verrucous lesion. At approximately this time a similar warty lesion appeared over the right ankle following a traumatic injury. One year later a similar verrucous lesion appeared over the midback. All lesions slowly increased in size. He consulted his family physician, who on April 2, 1951, prescribed a saturated solution of KI (potassium iodide) orally. This was continued for four and one-half months, reaching a dosage of 70 drops three times a day. He also received 850 r of x-rays in divided doses to the involved cutaneous areas. The patient believed slight improvement occurred in the lesions on this regimen, but he continued to lose weight (30 lb. in the three months prior to admission) and have night sweats, so he was referred to University Hospital.

On examination, Sept. 4, 1951, three areas of skin, the midback, the right wrist, and the right ankle, were involved with lesions characterized by elevated actively growing verrucous borders and reddish bases. Purulent material could be expressed from multiple pin point abscesses about the border of all lesions. There was scarring in the center of all lesions except the one over the right ankle (Fig. 3). An enlarged nontender, freely movable, lymph node

was present in the left axilla and inguinal region. The remainder of the physical examination gave normal results except for glycosuria and hyperglycemia.

Direct KOH mounts of sputum and pus taken from all three cutaneous lesions presented large numbers of budding organisms of B. dermatitidis. Cultures of sputum and cutaneous pus were also positive for B. dermatitidis. Blood and urine were normal except for an elevated fasting blood sugar and glucosuria. A skin test with blastomycin was positive.

A patchy increased density of the upper lobe of the right lung and an ill-defined area of increased density of the upper lobe of the left lung were demonstrated by x-ray (Fig. 4). Bone x-rays showed no osseous involvement. The x-ray findings were compatible with a diagnosis of pulmonary blastomycosis.

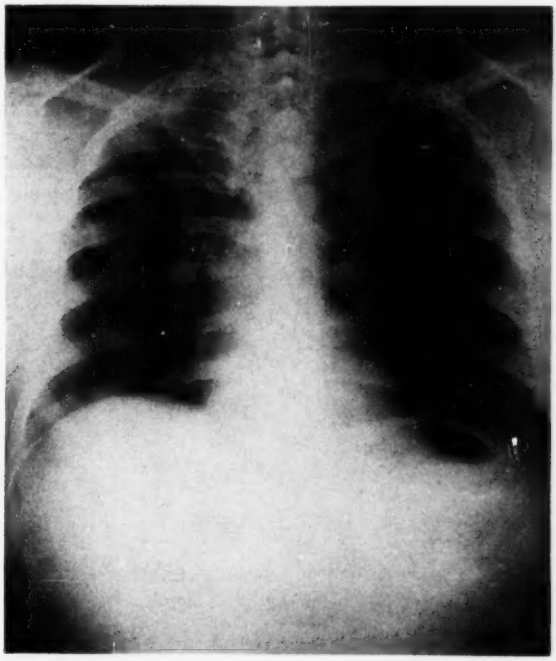

Fig. 4 (Case 3).—X-ray of chest showing bilateral pulmonary infiltration, worse on right. Sputum contained many B. dermatitidis organisms.

Two biopsy specimens of the cutaneous lesions showed inflammatory papillomatous hyperplasia, but no organisms were seen in the tissue. The pathological picture was compatible with blastomycosis, even though organisms were not seen.

After the secondary infection was controlled with wet dressings, a course of stilbamidine, 150 mg. given intravenously in 200 cc. of 5% dextrose every day for 12 days, was begun. Dramatic clinical improvement of the cutaneous lesions occurred during and after this treatment, but cultures of sputum and cutaneous pus were still positive for B. dermatitidis; so a second course of stilbamidine was given the patient after a one month interval.

The second course was dicontinued after the eigth intravenous injection of stilbamidine because of leucopenia. Complete healing of the cutaneous lesions occurred following the second course of the drug and the patient has since remained symptom-free (Fig. 5). Cultures and direct examination of sputum and from the healed cutaneous lesions have been negative. There was improvement of the lungs, but fibrosis was still present. The patient's diabetes mellitus

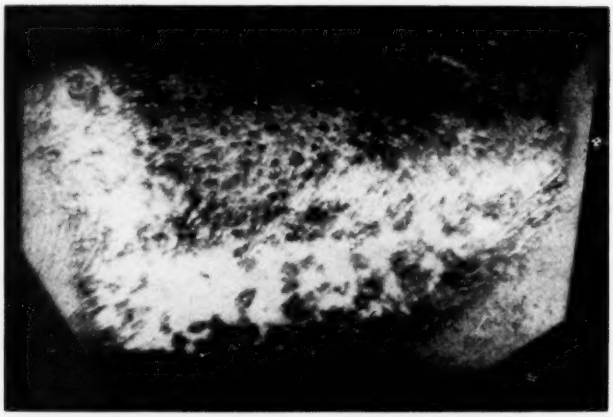

Fig. 5 (Case 3).—Right wrist after two courses (18 injections) of 150 mg. of stilbamidine. Cultures were negative.

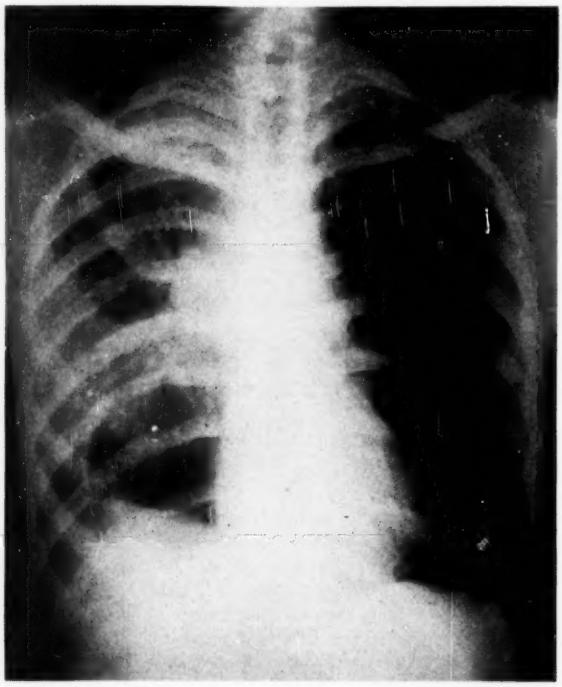

Fig. 6 (Case 4).—X-ray of chest showing marked pulmonary infiltration on right side. B. dermatitidis organisms were abundant in sputum.

has been well controlled with small amounts of insulin. He was last seen March 30, 1952, and had gained 30 lb. (13.6 kg.) in weight and had been working since discharge from the hospital.

CASE 4.—G. G., a 38-year-old Negro laborer, first had fever, night sweats, chills, weakness, weight loss, dyspnea, and a cough productive of mucopurulent sputum in March, 1948. He was hospitalized for influenza in Grand Rapids, Mich. However, the severity of his symptoms increased, and he was transferred to University Hospital.

Upon admission, May 21, 1948, the patient was febrile and his skin was dry and scaling owing to ichthyosis but otherwise normal. There were signs of consolidation over the right lower chest (Fig. 6). Bilateral nontender axillary lymphadenopathy was present. During his first period of hospitalization the first of many subsequent cutaneous lesions developed below the right scapula.

Fig. 7 (Case 4).—X-ray of left humerus, radius, and ulna showing decalcification of bone due to the infection.

Direct examination and cultures from his sputum were positive for B. dermatitidis. Other laboratory findings were normal except for an anemia (10 gm. of hemoglobin per 100 cc., 3,270,000 red blood cells, and an elevated white blood cell count of 10,000 per cubic millimeter). The blastomycin skin test was negative.

His chest roentgenograms revealed an extensive zone of increased density occupying all of the lower lobe of the right lung, with pleural thickening of both bases and apices.

A biopsy specimen of the first cutaneous lesion, which appeared below the right scapula during his first hospitalization, contained numerous organisms and was consistent with the pathological architecture of blastomycosis. Many biopsies of subsequent developing cutaneous lesions also showed B. dermatitidis.

During the patient's first hospital admission, from May 21, 1948, to Sept. 1, 1948, he had gradual but definite symptomatic improvement during treatment with a saturated solution of

KI (5 cc. three times a day) and cycloheximide (acti-dione®), 20 mg. then 40 mg. per day intramuscularly. He was also given 800 r of x-rays to the right lower lung field. After discharge from the hospital, many new cutaneous lesions subsequently developed over the trunk, some of which were cauterized. His dyspnea, cough, and weight loss increased, however, and he was again hospitalized. On the second hospital admission (May 16, 1949 to Sept. 15, 1950) a fluctuant tender mass was found just to the right of the vertebral column at the level of the sixth to ninth thoracic vertebrae. X-rays of this area showed extensive bony destruction. Destructive osseous lesions were also present in the fourth to ninth right ribs posteriorly. The new cutaneous lesions of the trunk and face which were present were positive on direct mount for B. dermatitidis. The organisms were also demonstrable in the urine. During hospitalization, urinary retention due to a blastomycotic prostatic abscess developed, and a transurethral resection

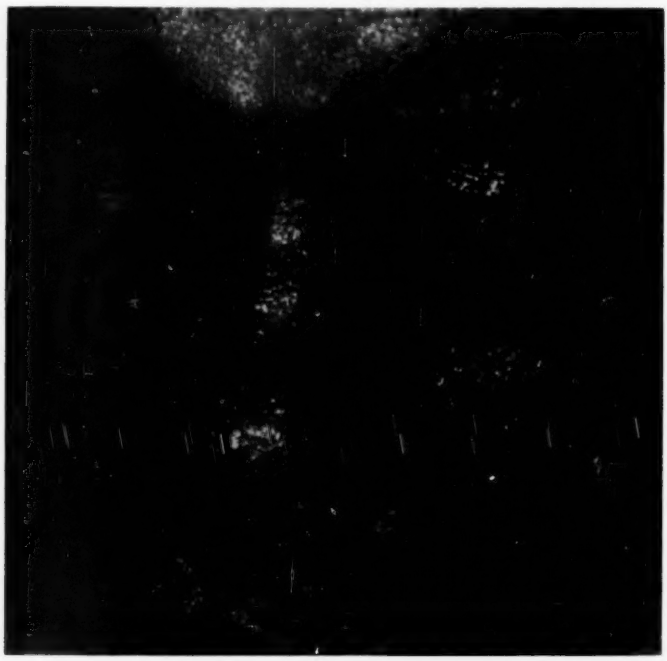

Fig. 8 (Case 4).—Face of man with many cutaneous lesions, involvement of lungs, lymph nodes, and bone before stilbamidine therapy.

was performed. A large fluctuant subcutaneous mass also developed over the right anterior leg. Various drugs were given the patient during his second admission. These included cortisone, 1.8 gm. over a two-week period; an extract of Bacillus subtilis (X-G) given by inhalation, and large amounts of both penicillin and chloramphenicol. No response was noted to these drugs, and the patient became progressively worse until treatment with saturated solution of KI was resumed. Again gradual improvement was noted clinically and symptomatically. At the time of discharge on Sept. 15, 1950, the subcutaneous abscesses and cutaneous lesions had healed. The sputum still remained positive for B. dermatitidis. He was discharged with instructions to continue use of KI, 60 drops four times a day.

The third admission (Jan. 24 to Nov. 15, 1951) was necessitated by the appearance of new draining subcutaneous lesions over the right heel and sternum and the demonstration by x-rays of an extension of the pulmonary and osseous disease. These findings occurred while the patient

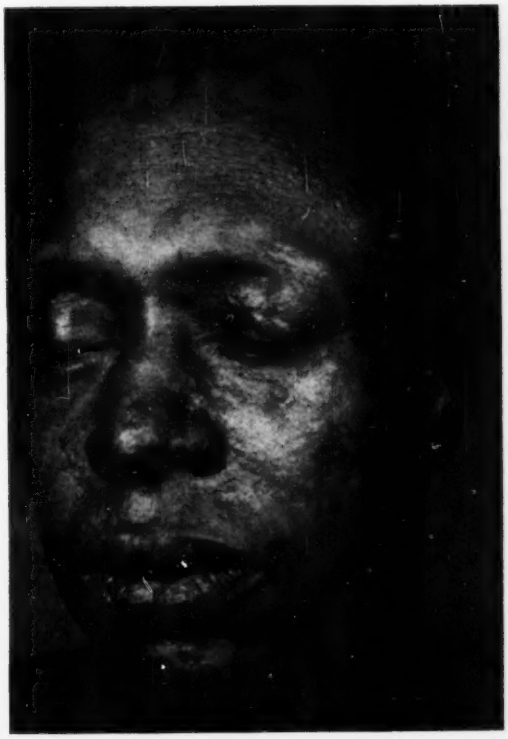

Fig. 9 (Case 4).—Patient two and one-half months later, after three courses of stilbamidine (3.9 gm.).

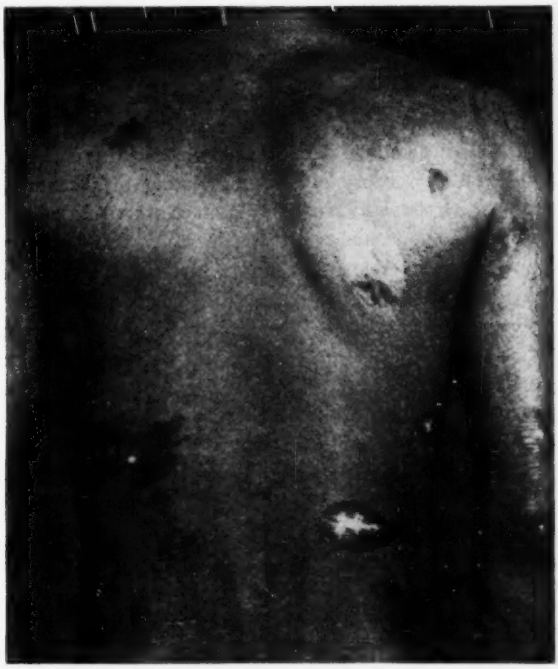

Fig. 10 (Case 4).—Back, taken at same time as *A*. Many healed scarred areas are present.

was taking KI. There was progressive increase in the bony (Fig. 7) and cutaneous disease (Fig. 8). So great was the extensive destructive involvement of the left humerus that amputation of the left arm was advised by the orthopedic surgeons. This was refused by the patient. Treatment while the disease continued to progress consisted of use of sulfadiazine, 5.0 to 6.0 gm. a day, plus KI, 24 cc. per day.

In August, 1951, treatment with stilbamidine was started with a dosage schedule of 100 mg. in 1,000 cc. of 5% dextrose given intravenously over a period of eight hours each day for six days. A second course of stilbamidine, 150 mg. per day for 12 days, was started Sept. 11,, and a similar day course was given Oct. 13 to 23, 1951. Slight improvement in the cutaneous lesions had been noted prior to stilbamidine therapy. Within two weeks following the first administration of stilbamidine, however, a definite improvement in all symptoms and clinical findings developed. The patient felt better, gained weight, and was up and about his room. For the first time since the onset of the disease, definite healing of bone was demonstrated by x-rays. However, B. dermatitidis was still present in the sputum. At the time of discharge on Nov. 14, 1951, the patient was free of all cutaneous lesions (Figs. 9 and 10). His improvement was maintained for three weeks after discharge, when the sites of several healed lesions over the trunk and left elbow became fluctuant and began to drain pus. B. dermatitidis was cultured from this pus and demonstrated in the sputum by direct mount. His left arm was out of its cast and was a good functioning extremity. Bone healing still progressed, and his lung had shown improvement by x-ray. He was again hospitalized (Jan. 2 to Jan. 31, 1952), and a fourth course of stilbamidine was administered. This consisted of 150 mg. per day in 200 cc. of 5% dextrose given intravenously for a total of 22 days. The draining lesions healed, and further healing of bone was demonstrated by x-ray. At the time of the last discharge, organisms were neither seen in nor cultured from the sputum. The skin was free of all involvement.

TOXICITY

The aromatic diamidines have been used in the treatment of several thousand patients, many of whom were poor risks because of their trypanosomiasis. No fatalities have been recorded from the drugs.

A nitritoid-like reaction occurs often immediately after the injection of these drugs.[8] These reactions are essentially eliminated by diluting the drugs to volumes of 250 cc. or more and giving them by slow intravenous drip.[9] Intramuscular injections are also associated with few reactions.

Late reactions are unique and occur in a fairly high per cent of patients treated. Two to five months after a course of stilbamidine, patients gradually observed the appearance of progressive sensory changes consisting of paresthesia, anesthesia, hypalgesia, and numbness confined usually to the face area.[4] Examination invariably revealed the presence of dissociated anesthesia in which there was decreased sensibility to light touch but pain, temperature, and pressure sense were intact. The trigeminal distribution radiating from the tip of the nose in a centrifugal pattern was usually involved.[4] On occasion the same findings have been reported to extend to the neck and waist. Some patients have shown slight loss of pain sensation. Often these symptoms slowly disappeared after a period of several months, but in others they seemed to persist indefinitely.[4] In the largest series, Sen Gupta [10]

8. Adams, A. R. D.: Studies in Chemotherapy: A Case of Indian Kala-Azar Treated with 4:4'-Diamidine Diphenoxy Pentane, Ann. Trop. Med. **35**:53-54, 1941.

9. Lourie, E. M.: Treatment of Sleeping Sickness in Sierra Leone, Ann. Trop. Med. **36**:113-131, 1942.

10. Sen Gupta, P. C.: Observations on the Neuropathic Sequel of Diamidino-Stilbene Therapy in Kala-Azar, Indian M. Gaz. **78**:537-543, 1943.

reported 17 instances of neuropathy among 104 patients followed. It is likely that the actual incidence of neuropathy is higher when cases are followed carefully.

The mechanism of stilbamidine neuropathy is totally obscure. Dosage, route of administration, speed of injection, and severity of immediate reactions do not appear to influence the occurrence of this complication.[10] Sen Gupta [10] postulated that a lesion was produced in the principal sensory nucleus of the trigeminal nerve. In support of this contention are the findings of Oastler and Fidler [11] that dogs showed marked pathological changes in the meninges, cerebrum, and brain stem which appeared to be secondary to vascular spasm or anoxia.

COMMENT

The chemical similarity of diethylstilbestrol and stilbamidine would encourage the theory that the two compounds have similar biological effects. In the comparison of these two substances with other steroids for their effect on B. dermatitidis, stilbamidine showed inhibition in dilutions as low as 0.01 mg. per milliliter of medium and the next most effective substance was diethylstilbestrol. Why diethylstilbestrol is more fungistatic in nutrient agar incubated at 37 C. than on Sabouraud's medium at room temperature is not known. More extensive in vitro studies are now being done on the stilbene group of drugs to determine their fungistatic qualities on the organisms which cause both the superficial and the deep mycoses. Their mode of action is likewise unknown and is the subject of further study.

Many substances are fungistatic when studied in vitro. When given orally they may be destroyed by the gastrointestinal secretions; when given parenterally, they may be toxic or may be conjugated into valueless compounds. The proof of effectiveness of any fungistatic agent lies in its therapeutic use in both animals and man.

The first two patients (Cases 1 and 2) had no treatment other than diethylstilbestrol. Although they had cutaneous blastomycosis only, their lesions promptly regressed and to date are free of any infection. The Negro automobile worker (Case 3) who was treated by two courses of stilbamidine (3 gm.) was shown at the March 30, 1952, meeting of the Detroit Dermatological Society. His cutaneous lesions had all healed, and he had no evidence of any infection by direct examination and culture of his sputum and skin lesions. He had gained 30 lb. in weight and had been at work since his hospital discharge.

The laborer (Case 4) has had, after a dramatic initial response, two mild relapses of some of his skin lesions, and in each instance organisms were demonstrated by direct examination and culture from them. His pulmonary symptoms disappeared after the third course of stilbamidine (3.9 gm.). There was evidence of improvement in his chest x-rays, and his sputum became negative for B. dermatitidis organisms. His bone lesions likewise have continued to heal. With each mild exacerbation of some of his cutaneous lesions, there has not been evidence of recrudesence of either his pulmonary or his bone disease. Likewise, after each relapse of his skin lesions he has promptly responded to the drug. It is not known

11. Oastler, E. G., and Fidler, H. K.: Cerebral Lesions Produced in Healthy Dogs by Intravenous Injection of 4:4'-Diamidino Stilbene, Tr. Roy. Soc. Trop. Med. & Hyg. **39**:533-538, 1946.

for how long or in what dose stilbamidine should be given. This patient may need larger amounts of the drug and over a longer time.

In none of the patients treated with stilbamidine have any toxic symptoms or signs occurred, and neither has there been any hormone effect, such as gynecomastia or changes in libido.

It is evident that more work both in vitro and in vivo must be done with this group of drugs before their total value in the mycotic diseases will be known. The clinical effect of the diamidines compared with the in vitro observations makes it apparent that one is dealing not with simple hormonal changes but with actual antimicrobial chemotherapeutic effects.

What the result of the use of the aromatic diamidines will be against other fungi and fungus diseases must be determined. They may be as specific for certain fungus diseases as penicillin is for certain bacterial infections. It appears, from our preliminary work, that their spectrum of effectiveness will be narrow in fungus diseases. Their use in treating blastomycosis seems very encouraging.

SUMMARY

Two men with cutaneous blastomycosis treated with 3 mg. of diethylstilbestrol daily had complete disappearance of their lesions in three to four months.

Two patients with systemic blastomycosis had rapid improvement of their disease after 3.0 gm. and 7.2 gm. respectively of stilbamidine. The first patient with pulmonary, lymph node, and skin lesions has remained well and culturally negative for four months after treatment. The second patient with pulmonary, lymph node, and bone lesions has had two mild cutaneous relapses but has remained culturally negative and asymptomatic from the pulmonary disease and has shown continued bone healing.

The fungistatic effect of diethylstilbestrol and stilbamidine in vitro is reported on Blastomyces dermatitidis.

The stilbene compounds offer an entirely new approach to the treatment of blastomycosis.

ABSTRACT OF DISCUSSION

J. LAMAR CALLAWAY, Durham, N. C.: All of us are indebted to Drs. Curtis and Harrell for calling to our attention again the use of stilbene derivatives in cutaneous and systemic blastomycosis, diseases which hitherto have been relatively unsuccessfully treated with iodides, x-ray therapy, curettement, and supportive systemic measures.

Clinical experience at Duke Hospital parallels the results of Drs. Curtis and Harrell in that one patient with cutaneous blastomycosis, one with laryngeal, and two with pulmonary have responded well to intravenous injections of stilbamidine in doses of 150 mg. in 200 to 250 cc. of fluid given intravenously daily. Results have been best when the patients were treated for about three weeks, given a rest period of 10 days or two weeks, and then had the course of therapy repeated. We have not used diethylstilbestrol in the treatment of any type of blastomycosis but believe the effect of stilbamidine is chemotherapeutic rather than hormonal.

The only reactions we have observed have been insignificant in that there has been a slight drop in the total white cell count but no significant change in the differential formula and occasionally bradycardia. In vitro studies carried out by Dr. Norman F. Conant in our mycology division have substantiated in general the reports of Drs. Curtis and Harrell. All cultures of B. dermatitidis were incubated at 37 C. and concentration of 0.025 mg. per milliliter of stilbamidine completely inhibited the growth of the Blastomyces. The concentration of 0.01 mg. per milliliter gave only a slight growth. "Propamidine" was about as effective as stilbamidine in a

concentration of 0.025 mg. per milliliter but not as effective at 0.01 mg. per milliliter. Pentamidine was essentially ineffective, and phenamidine was effective only in a concentration of 0.1 mg. per milliliter.

Candida albicans unfortunately is not affected in vitro by any of the stilbene derivatives studied. Cryptococcus neoformans and Histoplasma capsulatum both responded well in vitro to "propamidine," and we have one patient with Cryptococcus neoformans who is apparently responding well to "propamidine" therapy.

Although our in vitro experience showed stilbamidine to be about one dilution less effective than was reported by Drs. Curtis and Harrell, nevertheless, clinically our results have been extremely encouraging, and it appears that the stilbene derivatives offer real promise in the control of blastomycosis and possibly cryptococcosis and Histoplasma infections.

Dr. Arthur W. Stillians, Chicago: I want to thank Dr. Curtis for the excellent paper and for the fact that we have been able to benefit by his experience. I can report only one case, but an interesting one, that of a man who came to the Municipal Tuberculosis Sanitarium in Chicago a few years ago with a pulmonary involvement. Soon after he entered the sanitarium, blastomycosis developed, forming a large granuloma on the nose and pustules like the one that was just shown on his face and scalp, also containing Blastomyces.

We were puzzled about what to do. The internists did not want us to use iodides, but we used copper and got no improvement. Finally the internists agreed to a cautious use of iodides, under which the lesions cleared up quite well without any bad effect on the patient's pulmonary condition. When he was given streptomycin with potassium iodide there was a decided improve-

In Vitro Studies of Effect of Stilbene Derivatives on B. Dermatitides

	Concentration, Mg./Ml.					
	0.1	0.05	0.025	0.01	0.005	0.001
Stilbamidine	.....	.....	.....	+	++	+++
Propamidine	.....	.....	+	++++	++++	++++
Pentamidine	++++	.....	++++	++++	++++	++++
Phenamidine	.....	.....	.....	++++	++++	++++

ment of his general condition, but the blastomycosis recurred whenever we stopped using the iodides. We tried various other substances, among them ethyl vanillate, which gave no results, and then we used stilbamidine. On two courses of this drug the eruption cleared and has remained clear for six weeks without any untoward effect on the systemic condition. The patient's liver was full of amyloid for some time before his treatment with stilbamidine, but it has not caused any clinical symptoms. From the stilbamidine he has a paresthesia of the center of the face. This is slowly clearing.

Dr. Marion B. Sulzberger, New York: I, too, want to thank Dr. Curtis for an excellent presentation, most instructive and most promising. I should like to ask him against just which of the ordinary dermatophytes he has tested these drugs. The feasibility of using stilbamidine and derivatives of the stilbene group was brought to my attention by Dr. I. Snapper in New York several months ago, but, unfortunately, at that time we had no patients with systemic blastomycosis on whom to try them out. We hesitated to try out this series of chemotherapeutic agents on superficial fungous infections of the skin, hair, or nails because of the untoward effects, including fifth nerve involvement, which, as Dr. Curtis said, can apparently be permanent. Now, there is a new preparation which has come out recently—dihydrostilbamidine, I believe—which, it is said, does not produce these side-effects. I should like to ask Dr. Curtis what he knows about this preparation and whether he has had the opportunity of using it.

Dr. Arthur C. Curtis: I wish to thank my discussors. Emphasis of the chemotherapeutic effect of stilbamidine and diethylstilbestrol by Dr. Callaway saved me discussing this subject during the presentation of the paper. From the work we have done I believe these drugs act on B. dermatitidis by a chemotherapeutic and not by hormone effect. No hormone side-effects were noticed in any of the patients who had stilbamidine, and we have not heard of such an effect in other cases in which it has been used.

In one patient the white blood cell count fell below 3,000 per cubic milliliter (Case 3) after eight injections of stilbamidine. We thought it wise to stop the treatment then. I haven't noticed bradycardia in our patients, but I don't think I have looked for it. I can also substantiate what Dr. Callaway said about C. albicans. Unfortunately, C. albicans grows very well in the presence of these drugs. I was pleased to hear of Dr. Stillians' case and the beneficial results he obtained.

Dr. Sulzberger asked what the effect was of these drugs on the superficial fungi. We are now doing a complete in vitro study of the effect of these drugs on the organisms that produce both the superficial and the deep fungous infections, and I am not yet prepared to give any final results of their effect. This study will be reported separately. Elson's report on the in vitro effect of antibacterial and fungistatic properties of "propamidine" shows it to be effective in some of the superficial fungi.[3]

Whether dihydrostilbamidine will cause a decrease in the incidence of damage to the sensory part of the fifth nerve is not yet known to me.

CANDIDA ALBICANS

Rapid Identification in Pure Cultures with Carbon Dioxide on Modified Eosin-Methylene Blue Medium

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RECENT reports [1] of infections with Candida (Monilia) albicans following the use of antibiotics suggest the desirability of a simple, rapid, and reliable method for the differentiation of this fungus from the common closely related nonpathogenic species of the same genus. The procedure now in use requires considerable laboratory manipulation extending over several days. The method here described is a combination of simple techniques already familiar in clinical laboratories. It yields readily interpreted results in 18 hours. The fungus can be identified either in pure culture or in mixed cultures made directly from feces, mucous membranes, or skin. This paper describes only the results obtained with pure cultures. Use of the method with clinical specimens will be reported in another communication.

The culture medium is Levine eosin-methylene blue agar (difco®). To this is added a solution containing 10 mg. per cubic centimeter of crystalline aureomycin hydrochloride. The aureomycin solution in the proportion of 1 cc. per 100 cc. of agar is added before the plates are poured. It prevents the growth of Gram-negative bacteria but does not inhibit the characteristic development of C. albicans or of the other species of Candida used in this study. Plates are prepared in advance by pouring 4 cc. of the sterile medium into sterile 5 cm. Petri dishes and drying by incubation at 37 C. for 24 hours. After drying, the plates may be stored in the refrigerator until needed. They are then inoculated from pure cultures by streaking with thin saline suspensions.

For incubation, the plates are placed in an atmosphere of about 10% CO_2, conveniently produced by the method described by Cohen and Fleming.[2] Concentrations of 5 to 20% have been found to be equally effective. In our laboratory we use

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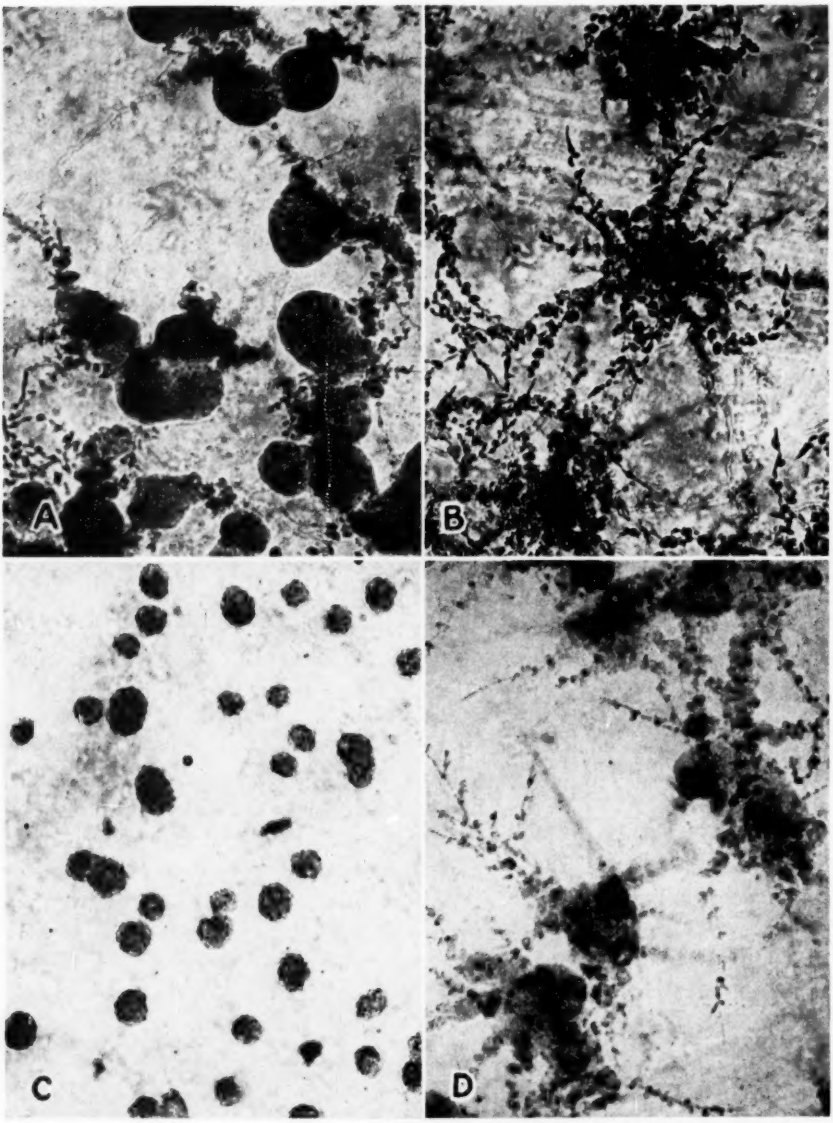
1. (*a*) Tomaszewski, T., and Paznan, M. D.: Side-Effects of Chloramphenicol and Aureomycin, with Special Reference to Oral Lesions, Brit. M. J. **1**:388, 1951. (*b*) Woods, J. W.; Manning, I. H., Jr., and Patterson, C. N.: Monilial Infections Complicating the Therapeutic Use of Antibiotics, J. A. M. A. **145**:207, 1951.

2. Cohen, M. B., and Fleming, J. S.: The Diagnosis of Epidemic Meningitis and the Control of Its Treatment by Rapid Bacteriologic and Serologic Methods, J. Infect. Dis. **23**:337, 1918.



C. albicans, 18 hours at 37 C on eosin methylene blue medium; × 56. *A*, typical strain grown in air; *B*, same typical strain grown in 10% CO_2; *C*, atypical strain grown in air; *D*, same atypical strain grown in 10% CO_2.

a wide-mouth glass-stoppered jar of 2,500 cc. capacity. Into this jar, along with the inoculated plates, is placed a beaker containing 1 gm. of $NaHCO_3$. Seven cubic centimeters of 5% H_2SO_4 is added to the $NaHCO_3$. The jar is quickly closed and kept closed until the CO_2 gas has stopped bubbling. The cover is lifted slightly to relieve the excess pressure, and the jar is then sealed with "plasticine" and placed in the incubator at 37 C.

If C. albicans is present, its colonies can be identified within 18 hours, either microscopically or with a × 6 hand lens. The colonies are distinctly unlike those of any of the seven other Candidas tested and are characterized by an easily recognized spidery or feathery mycelium (Fig. *A* and *B*). Under higher magnification (× 56), the spidery colonies of C. albicans are seen to consist of irregular masses of clear, oval cells, from which radiate one or more filaments of mycelium of varying length tapering off to bare ends. Along these filaments are found small clusters of spores. Many of the filaments are seen to penetrate deep into the agar. In the feathery type of colony, the central mass of cells is smaller than that of a spidery colony. It appears as a dark mass of furry brown in which the individual cells are indistinct. This dark, furry appearance is perhaps due to the massing of young mycelium spores in the central area. Each colony is entirely encircled (and probably covered) by a fringe of long filaments bearing small spore clusters, the branches tapering off to long bare ends. Transplanted first to Sabouraud's agar and then to corn meal agar, cultures made from either spidery or feathery colonies on Sabouraud's agar always show within four days at 24 C. the characteristic chlamydospores usually accepted as diagnostic for C. albicans.

Under the conditions here described, only one of the other Candida species studied,[3] namely, C. stellatoidea, showed mycelium, and this was composed of a loose network of scattered spores with long intertwining tubes (without the formation of colonies), not in any way to be confused with C. albicans. C. stellatoidea produced the same type of growth without CO_2, which also differentiated it from C. albicans.

Mycelium-inducing effects of CO_2 were reported by Langeron and Guerra in 1938.[4] The importance of incubation with CO_2 in this method is indicated by control experiments in which 45 different strains of C. albicans were grown in air rather than in 10% CO_2. After 18 hours, most of the dispersed colonies in 36 (80%) of the strains tested showed the typical spidery growth referred to above. (These spidery colonies grown in air were about half the size of those grown in CO_2.) The remaining nine strains (20%) incubated in air were atypical in their growth, producing no mycelium, and were therefore not readily identifiable under these conditions (Fig. *C*). If transferred to a 10% CO_2 environment, however, all the atypical strains yielded the same type of spidery growth as the typical strains grown in air (Fig. *D*). It is noteworthy that the mycelium-inducing effect of CO_2

3. These were C. mortifera (1 strain), C. krusei (3 strains), C. stellatoidea (3 strains), C. lipolytica (1 strain), C. tropicalis (2 strains), C. guilliermondi (3 strains), C. parapsilosis (4 strains) and three unidentified yeasts.

4. Langeron, M., and Guerra, P.: Nouvelles recherches de zymologie médicale, Ann. parasitol. **16**:429, 1938.

was observed only in cultures incubated at 37 C. and not in cultures kept at 24 C. At the lower temperature, neither the typical nor the atypical strains produced mycelium, even when supplied with CO_2. Cultures on Sabouraud's agar or on 1% dextrose bacto-agar did not show filamentation in response to CO_2. Further work will be required in order to determine what factors permit C. albicans to produce the filamentation effect in the eosin-methylene blue medium but not in the others. It is clear that when used both with 10% CO_2 and with incubation at 37 C. the modified eosin-methylene blue medium permits the identification as C. albicans of any strain, either typical or atypical. In a subsequent paper it will be shown that the same method can be successfully used for the identification of C. albicans in clinical specimens.

Dr. Rhoda Benham supplied pure cultures of the various species of Candida.

CHROMOBLASTOMYCOSIS (MYCETOMA FORM) TREATED BY SURGICAL EXCISION

Correction of Defect by Cross Leg Pedicled Flap

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CHROMOBLASTOMYCOSIS is a chronic infectious disease of the skin characterized by nodular, verrucous, or cauliflower-like lesions. Extension from the skin to the subcutaneous tissues occurs at times, and, although the infection usually is confined to the lower extremities, it may involve the hands and arms. The disease is caused by what appears to be one fungus or several closely related fungi.

It is accepted generally that chromoblastomycosis was first recognized by Pedroso,[1] of São Paulo, Brazil, in 1911, but the first comprehensive descriptions of the disease were published by Lane [2] and Medlar [3] in 1915. Many different names have been suggested for the lesion, but the one in popular use today is chromoblastomycosis, originated by Terra and associates in 1922.[4] This term would seem to indicate an association of pigment formation and blastomycosis and would thus be misleading, for, although pigmentation is produced, chromoblastomycosis differs from blastomycosis not only in etiology but also in clinical and pathological findings. Chromoblastomycosis is a lesion confined to the skin and subcutaneous tissues without associated systemic manifestations, and it is not fatal. Blastomycosis, beginning as a localized lesion, eventually disseminates and causes death from systemic involvement.

A variety of names for this disease has been offered by a number of authors. These are *blastomycose negra,* suggested by Pedroso [1] in 1911; *dermatite verrucosa por Phialophora verrucosa,* by Pedroso and Gomes [5] in 1920; *chromomycosis,* by

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1. Pedroso, A., cited DaFonseca, O., and Area Leao, A. E.: Las cromoblastomicosis, Quinta reunión Soc. argent. de pat. reg. **1**:329, 1911.

2. Lane, C. G.: A Cutaneous Lesion Caused by a New Fungus (Phialophora Verrucosa), J. Cutan. Dis. **33**:840, 1915.

3. Medlar, E. M.: A Cutaneous Infection Caused by a New Fungus, Phialophora Verrucosa, with a Study of the Fungus, J. M. Res. **32**:507, 1915.

4. Terra, F.; Torres, M.; DaFonseca, O., and Area Leao, A. E.: Novo typo de dermatite verrucosa, mycose por acrotheca, com associacão de leishmaniosa, Brasil-méd. **36**:363, 1922.

5. Pedroso, A., and Gomes, J. M.: Quatro casos de dermatite verrucosa, produzida pela Phialophora verrucosa, Brasil-méd. **34**:105, 1920.

Moore and Almeida [6] in 1935; *dermatite verrucosa cronomicosica*, by Redaelli [7] in 1935; dermatitis verrucosa blastomicotica, by Boggino [8] in 1937; Pedroso's disease, Fonseca's disease, or Gomes' disease, by Weidman and Rosenthal [9] in 1941, and Pedroso and Carrión's disease, by Barros-Barreto [10] in 1945.

A review of the literature shows that 151 authentic cases of chromoblastomycosis have been reported. The majority of these (119 cases) occurred in tropical climates, and 32 cases were reported from subtropical areas. The largest groups were reported from Cuba (43) and from Brazil (41), but the disease has been reported from all parts of the world with the exception of Asia. Nine cases of chromoblastomycosis have been observed in the United States; of these, one each occurred in Massachusetts, North Carolina, New York, Texas, Florida, Georgia, and Pennsylvania; two occurred in Missouri. The present report, the ninth case from the United States, is an instance of verified chromoblastomycosis in an American who had never been outside the continental United States. A cure in this case was obtained by radical excision of diseased tissue. The defect on the outer aspect of the ankle and foot was successfully treated by transplantation of a pedicle of skin and subcutaneous tissue from the opposite leg. The detailed presentation of this case appears justified in view of the paucity of reports of chromoblastomycosis and because of the rehabilitation secured by radical excision and reconstructive surgery.

REPORT OF A CASE

W. A., a 44-year-old Negro longshoreman, was admitted to the New York Hospital on Aug. 30, 1949, with a chronic granulomatous lesion on the lateral aspect of the left foot (Fig. 1). In his work he had contact with cargos from ships coming from many ports of the world. Born in Georgia, he had spent his life along the Atlantic seaboard between his home state and New York. Approximately three years before admission, he sustained an abrasion on the side of his foot while unloading a coal ship. A fissure developed from which purulent material drained. Although this healed, it left a tumor-like mass at the site of the abrasion. The surface of the mass had broken down at several points, and sanguinopurulent material escaped. The patient complained of a dull ache and moderate tenderness of the foot, which swelled on dependence. His general condition was good, and his past history and that of his family were unrelated to his complaint. The positive findings were confined to the left foot. The local lesion consisted of a moderately firm mass in the region of the lateral malleolus which measured 10 by 6 by 2 cm. It appeared to involve both skin and deeper soft parts. Scattered over its surface were soft purplish-black nodules from 0.2 to 0.5 cm. in diameter, some of which extended onto the sole. The skin surrounding the nodules was hyperkeratotic. The whole area was moderately tender; there was no increase in local temperature. The only soft points of the mass were the purplish papules. When their heads were removed, sanguinopurulent fluid was exuded which contained small angular black bodies, 0.3 to 1 mm. in diameter. No similar lesions were found elsewhere on the body. Roentgenograms of the foot showed no involvement of underlying bone. A chest x-ray

6. Moore, M., and de Almeida, F. P.: New Organisms of Chromomycosis, Ann. Missouri Bot. Gard. **23**:543, 1936.

7. Redaelli, P.: L'Attuale sistemazione delle cosidette "blastomicosi," Rev. sudam. endocrinol. **19**:85, 1936.

8. Boggino, L.: Dermatitis verrucosa blastomicótica: primera observación paraguaya, Novena reunión Soc. argent. de pat. reg. **2**:1329, 1937.

9. Weidman, F. D., and Rosenthal, L. H.: Chromoblastomycosis: New and Important Blastomycosis in North America; Report of Case in Philadelphia, Arch Dermat. & Syph. **43**:62, 1941.

10. de Barros-Barreto, J.: A saúde pública no Brasil, Bol. Ofic. san panam. **24**:193, 1945.

showed no evidence of disease. Biopsy of the lesion and culture studies led to a pathological diagnosis of chronic infectious granuloma, consistent with the picture of chromoblastomycosis. Cultures of tissue and of the exudate revealed a fungus growth identified as Hormodendrum (Fonsecaea) pedrosoi. The growth characteristics were predominantly of Acrotheca type.

The patient was discharged from the hospital and treated with x-rays. With use of a 10 cm. cone, 150 r was given over the lesion every two weeks for four treatments. After three months of observation, no evident change in the infection had occurred.

The patient was referred by the dermatology service of Dr. George M. Lewis to the plastic surgery clinic for treatment on Jan. 24, 1950. Surgical excision and soft tissue reconstruction were recommended, but the patient delayed such treatment until April, 1950. At that time the lesion was excised en bloc. To insure complete extirpation without entering the infected area, it was necessary to expose tendons of the peroneus longus and peroneus brevis muscles and to partially remove the cruciate crural ligament and the extensor digitorum brevis muscle. The

Fig. 1.—Chromoblastomycosis of the foot of three years' duration.

large defect was covered by suturing into it a direct pedicle, elevated on the right thigh (Fig. 2). This pedicle was detached from the donor leg on the 21st postoperative day. Healing at the site of the lesion was without incident. The patient was provided with an elastic stocking and discharged on May 26, 1950. He was able to resume work. Two years after surgery there is no evidence of recurrence (Fig. 3).

ETIOLOGY

Medlar's [9] examination of tissue taken from Lane's patient in 1915 revealed a granulomatous lesion in which numerous spherical pigmented fungus cells were found. Cultures showed an organism producing a dark mycelium. Smears from the lesion revealed cup-shaped conidiophores producing spores. Thaxter,[11] after careful

11. Thaxter, R.: Mem. Acad. Arts & Science **15**:431, 1926.

Fig. 2.—Repair of defect. The lesion was excised en bloc together with a portion of the underlying cruciate ligament and the extensor digitorum brevis. The defect was corrected immediately by the use of a cross leg flap of skin and subcutaneous tissue as shown. The pedicle was divided 21 days later.

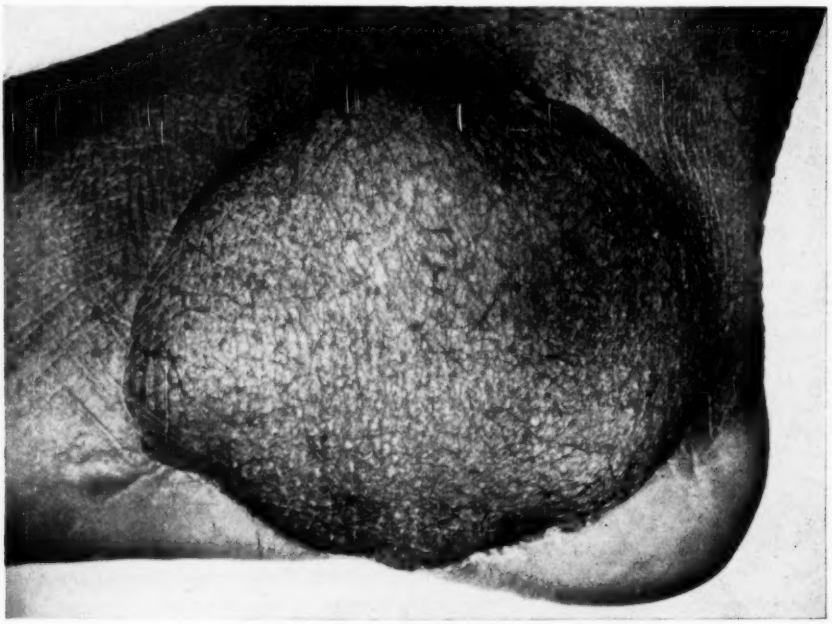

Fig. 3.—Appearance of the healed flap. There has been no recurrence of the disease in the two-year period of follow-up.

study of the organism, named it Phialophora verrucosa, a member of a genus not previously described.

From Medlar and Lane's descriptions it is apparent that in their case, which occurred in Massachusetts, the infection was similar to that observed by Pedroso in Brazil. Brumpt [12] in 1932 established the fact that the causative organism in Pedroso's case was not P. verrucosa but a new species which he called Hormodendrum pedrosoi, for the conidia were in branching chains, a characteristic of the Hormodendrum type of reproduction. Fonseca and Leao [1] conducted a careful study of isolated organisms taken from eight Brazilian patients and, like Brumpt, concluded that they were not members of Phialophora. They classified them in the genus Acrotheca, for they found terminal clusters typical of Acrotheca growth. They named the organism Acrotheca pedrosoi in 1923. Carrión [13] reported a study of fungus from a patient with chromoblastomycosis, which he called Hormodendrum compactum, the growth pattern of which consisted of subspores separated by wide septa and borne in branching conidial chains on simple or branched conidiophores.

In 1936 Negroni [14] studied a case of chromoblastomycosis from Argentina and found both Hormodendrum and Acrotheca types of sporulation. He used the term genus Fonsecaea to include organisms possessing the double type of sporulation, and the species became known as Fonsecaea pedrosi. Later Carrión and Emmons proved that this organism has a semiendogenous type of sporulation in which conidia were produced in phialides. Their discovery of this new and basic characteristic of the spores established a relationship to the originally described generic group, Phialophora.

It is considered likely, on the basis of these various studies, that one genus, H. (F) pedrosoi, is the etiological agent in chromoblastomycosis. The fact that it possesses four types of semiendogenous sporulation, with one type predominant, led to much taxonomic confusion and debate. Essentially the same clinical and pathological picture is displayed whatever type of sporulation predominates.

PATHOLOGY

Chromoblastomycosis presents a rather typical picture of infectious granuloma, in which the causative organism can be recognized macroscopically as well as microscopically. When the lesion is well developed, two different clinical pictures are observed; the commoner type appears to be directed outward with the formation of a papillomatous, sessile, or cauliflower-like growth and a granular surface. In this lesion the infection is limited to the epithelium and corium. In the less common variety of the lesion, it has the appearance of a mycetoma. Our patient presented this picture and a similar lesion involving the hand was reported by Lewis and associates.[15] Both were deep-seated tumor masses involving skin and deeper tissues. The slightly elevated surface faded into surrounding normal tissue without a distinct outline. The cauliflower type of growth is not seen in these mycetomatous lesions.

12. Brumpt, E.: Précis de parasitologie, Ed. 4, Paris, Libr. Acad. méd., 1927, p. 1333.

13. Carrión, A. L.: Chromoblastomycosis, Mycologia **34**:424, 1942; abstracted, Trop. Dis. Bull. **40**:410, 1943.

14. Negroni, P.: Estudio micologico del primer caso argentino de cromomicosis, Rev. Soc. argent. biol. **12**:180, 1936.

15. Lewis, G. M.; Hopper, M.; Sachs, W.; Corina, F., and Potelunas, C. B.: Mycetoma-like Chromoblastomycosis Affecting the Hand, J. Invest. Dermat. **10**:155, 1948.

The apparent explanation of the origin of these two clinical pictures is the site of deposition of the causative organism. If laid down in the subcutaneous tissue, a mycetoma occurs, whereas the infection beginning in the skin creates a more superficial papillomatous growth. In Lewis' case involving the hand the patient gave a history of a deep splinter wound; my patient suffered an abrasion of the foot, the depth of which was not determined. There seems to be no relationship between growth variant and type of lesion produced, whether verrucous or mycetomatous.

Chromoblastomycosis spreads very slowly and metastasizes rarely. In only 1 of the 151 cases in the literature did metastasis develop. In it the disease of the foot and leg persisted for 15 years before the metastatic lesion occurred. It lay deep in the tissues on the ulnar surface of the forearm and was attached to the bone, but it did not involve the overlying skin. Because of the lack of infection in the skin, it was concluded that the origin of the secondary lesion was metastatic and not due to autoinoculation. In contrast to this, in a case reported from Texas involving foot and ankle there were no metastases though it was observed over a period of over 40 years.

Apparently the lymphatics are not implicated in chromoblastomycosis. Meriine [16] found blastomycotic organisms in a lymph node from a patient with tuberculosis who showed no signs of chromoblastomycosis; culture studies, however, were not reported. No other case of this kind is found in the literature.

The common site of the infection is the ankle and foot, the hand being affected less frequently. If neglected, the lesion may spread slowly in the local area. It starts in the majority of cases as a small dull red or violet papule which gradually increases in size and assumes a sessile character and granular surface. Ulceration seldom occurs, and the surface of the lesion usually is dry and intact. Older lesions tend to fungate and acquire overhanging borders and show dirty crusts which bleed readily on abrasion. The skin in these long-standing infections becomes lymph-edematous.

A much simpler gross clinical picture is presented by the mycetoma-like lesion. Its bulk is firm and deeply situated. The elevated surface is usually dry and smooth save for the multiple violet-colored papules surrounded by concentric epithelial scaling. These papules represent sinus tracts, temporarily closed, which when broken open discharge sanguineopurulent material. This black exudate contains angular bodies known to be colonies of the infecting fungus.

The microscopic picture in the two lesions is identical except that they lie in different structures. The epidermis, markedly thickened by hyperplasia of the stratum Malpighii, is not only broader than normal but also sends irregular downgrowths into the corium. This fact explains why chromoblastomycotic lesions have often been mistaken for carcinoma of the squamous cell type. The stratum corneum shows marked hyperkeratosis, irregular and distorted in character. The epithelium is often infiltrated by leucocytes which may collect in large numbers to form miliary abscesses, but widspread necrosis is uncommon. Sinus tracts containing necrotic debris surrounded by polymorphonuclear leucocytes are seen coursing through the epithelium. This reaction is both focal and diffuse and in some areas is

16. Meriine, J. A.: Chromomycosis of the Skin, with a Lesion of Regional Lymph Nodes, Ann. dermat. et syph. **9**:122, 1938.

distinctly tuberculoid. There is a marked tendency to wall off the infected area by fibrosis, a fact which probably explains why a long-standing lesion fails to infiltrate neighboring tissues. In old lesions the center may assume a burned-out appearance.

The significant feature in the pathology of this lesion is the infecting organism. Hyphae are not found in tissue specimens. In stained sections the spores are seen to average 10 μ in diameter and to vary from round to oval or crescent. The color is variously described as ochre, olivaceous, yellow-green, or dark chestnut. Spores are found singly or in clusters scattered throughout the lesion and are sometimes present in the epithelium, in giant cells, in microabscesses, or in tuberculoid structures.

TREATMENT

Many methods have been used in the treatment of chromoblastomycosis, with little success. Chemotherapeutic agents such as arsenic, mercury, bismuth, gold, antimony, methylene blue, sodium iodide, and potassium iodide all have been tried but without effect. Because of their value in the treatment of blastomycosis, the iodides have been favored in treating the disease, and their use has been continued for longer periods than warranted by the results. In a case reported by Carrión and Koppisch [17] intravenous administration of sodium iodide under controlled hospital conditions was continued for two years with few interruptions to the therapy. The initial dose was 1 gm. daily, but when it was found that the patient had an unusually high tolerance for iodides the dose was increased to 9 gm. a day and was continued at this rate for two years. After the first year of treatment some of the older lesions healed, leaving brawny scars. In the second year there was neither regression nor progression of the infection. When the iodide therapy was interrupted temporarily toward the end of the second year, new lesions appeared. This extensive experience proved that iodides, even in massive dosage, do no more than to retard the progress of the disease. That any effect was derived from treatment in this case may be doubted, for without iodides chromoblastomycotic lesions remain localized over long periods and the older lesions tend to heal. In patients who were sensitive to the fungus antigen, iodides caused rapid increase in the severity of the disease, and desensitization was required before iodide therapy could be instituted. Iontophoresis with copper sulfate was used for seven and one-half months in a case of chromoblastomycosis involving the hand and arm. Clinical improvement occurred, but the lesion persisted, and the treatment was abandoned. Weidman and Rosenthal employed roentgenotherapy on five occasions in their case, but recurrences were noted one year and again four years after treatment. It was recognized by them that this therapy had not been beneficial. X-rays had no effect upon the patient reported by us. Fulguration is not a satisfactory form of therapy, for the scarring of tissues resulting from this treatment makes it impossible to determine the junction of pathologic and normal tissue. The wounds made by fulguration, as well as by curettage, usually heal by granulation, which means loss of time to the patient and excessive scar formation with a thin, weak epithelial covering. A patient from the

17. Carrión, A. L., and Koppisch, E.: Observations on Dermatomycosis in Puerto Rico; Report on Case of Chromoblastomycosis, Puerto Rico J. Pub. Health **9**:169, 1933.

Canal Zone with chromoblastomycosis involving the ankle was treated by curettement and electrodesiccation. The lesion recurred repeatedly but finally healed after seven months.

SUMMARY

A patient with chromoblastomycosis in the form of a mycetoma is presented. Surgical excision and plastic reconstruction resulted in a cure. Failure of other forms of therapy makes surgery the treatment of choice. In several reported cases cure has been accomplished by radical surgical extirpation. It is essential that the operation be so planned that the lesion is removed with a wide margin of healthy tissue, as in the treatment of carcinoma. To prevent reimplantation of the fungus, the tumor should not be cut into. In lesions of the skin and subcutaneous tissue, broad excision beyond the involved area requires closure by plastic surgical procedures. In deeper infections the muscles, nerves, and tendons may have to be sacrificed. The etiology, pathology, and treatment of chromoblastomycosis are discussed.

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PROCEDURE FOR EVALUATING SKIN-SENSITIZING POWER OF NEW MATERIALS

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WITH THE accelerated development of new drugs, cosmetics, dyes, and other materials which may contact the skin, there is an increased need for rapid screening methods for evaluating their sensitizing potentials. Animal tests have little utility, mainly because of species differences in sensitizability. The prophetic patch test procedure suggested by Schwartz and Peck [1] is of value but in some aspects is not entirely adequate for the purpose. In this test, the new material is applied to the skin for 48 hours under an occlusive patch; a group of 200 or more persons is used. The same group is retested in 14 to 21 days; new reactors are deemed to have been sensitized by the first patch test.

Among problems encountered in carrying out this test is, first, the difficulty in distinguishing between allergic and primary irritant patch reactions. With threshold irritants, there may be variation from time to time in reactivity of the subject, and the appearance of a positive reaction does not necessarily indicate sensitization. Second, except in the case of materials which are of the highest order of allergenicity (such as paraphenylenediamine and its derivatives), the prophetic patch test may give false negative results, since a single application to a small area of skin in no way resembles usage conditions for most substances, and often only a relatively low yield of sensitized subjects will be obtained by such contact. In addition, even if the test should reproduce conditions of actual use, statistical interpretation of the results may be difficult. With some materials, particularly cosmetics, a reaction rate as low as 1 : 1,000 may be entirely too high, and it is difficult to ascertain sensitization rates in this range with the prophetic patch test unless extremely large groups are tested. In this connection it has been shown by statisticians [2] that if the reaction rate in the general population is 1 : 1,000 in any random group of 200 sub-

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From the Department of Dermatology, University of Illinois College of Medicine, Francis E. Senear, M.D., Chairman (Dr. Brunner), and the Toni Research Laboratories, Chicago (Miss Smiljanic).

1. Schwartz, L., and Peck, S.: The Irritants in Adhesive Plaster, Pub. Health Rep. **50**:811-819, 1935; cited by Schwartz, L., and others: An Outbreak of Dermatitis from New Resin Fabric Finishes, J. A. M. A. **115**:906-911, 1940.

2. Henderson, C. R., and Riley, E. C.: Certain Statistical Considerations in Patch Testing, J. Invest. Dermat. **6**:227-230, 1945. Knudsen, L. F.: A Note on the Statistical Probabilities of Finding Hypertensive Subjects in Random Samples, ibid. **6**:231-232, 1945.

jects 82% will be nonreactors; likewise, even though no reactions are observed in a sample group of 200, it is still possible to have a reaction rate as high as 1.5% in the general population.

It is the usual clinical experience that eczematous sensitization may require a number of exposures for its genesis. The method to be presented (adapted from a procedure described by Sulzberger [3]) produces a high yield of sensitized subjects within a short time period and requires only small test groups. It utilizes the observations of Jadassohn [4] and others, who showed the importance of repeated applications of antigen in their attempts to produce sensitization in humans with simple chemicals. Briefly, the procedure consists in the repeated application to the skin of the test material under conditions resembling normal use rather than a single application as a patch test. The mode of application is, therefore, varied in accordance with the particular type of material tested. For example, in the case of mercaptans employed as hair-waving agents, the test materials were applied to the skin in use concentration for some 30 minutes, corresponding to the normal period of

Reactions at Sites of Test Applications

Applications	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Totals
Mercaptan A (16 persons)																
Accumulated no. of immediate, transient reactions	0	0	0	0	0	0	0	0	0	0	0	0	0	0	..	0
Reactions persisting 24 hr. or longer	0	0	0	0	0	1	1	1	2	3	4	4	4	4	5	5
Mercaptan B (10 persons)																
Accumulated no. of immediate, transient reactions	4	1	2	2	6	4	4	4	3	5	6	6	6	6	..	6
Reactions persisting 24 hr. or longer	0	0	0	0	0	0	0	0	0	0	2	2	2	4	..	4
Mercaptan C (35 persons *)																
Accumulated no. of immediate reactions	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Reactions persisting 24 hr. or longer	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

* One subject in this group had a positive standard patch test reaction at the termination of the experiment.

contact in permanent waving. Saturated gauze pads were used to insure uniform application. Applications were repeated daily for five days, a different area of forearm skin being used each day to eliminate a possible summation of primary irritant effects. No applications were made for the following seven days, during the period of incubation of sensitization. Applications were then begun again and continued until reactions developed or until the end of the test period at three weeks. The second series of applications was used both to demonstrate sensitization and to allow for repetition of contact required for high yields. Observed reactions consisted in the development of eczematous reactions lasting over 24 hours at the test sites and in some instances the simultaneous flare-up of distant previously tested sites. Concurrently, patch tests which were originally negative in all cases were shown to be positive. Three mercaptans were tested by this method.

3. Sulzberger, M. B.; Baer, R. L.; Kanof, A., and Lowenberg, C.: Methods for Rapid Evaluation of Beneficial and Harmful Effects of Agents Applied to Human Skin, J. Invest. Dermat. **7**:227-238, 1946.

4. Jadassohn, J.: Bemerkungen zur Sensibilisierung und Desensibilisierung bei den Ekzemen im Anschluss an einen Fall von Odolekzem, Klin. Wchnschr. **2**:1680-1684, 1923.

RESULTS

As indicated in the table, mercaptan A is not a primary irritant. By the sixth application, however, one subject began to show persistent eczematous reactions, and by the eleventh application four subjects were reacting. These reactions could not have been only of primary irritant nature, since simultaneously the reactors showed flare-ups at old sites of application and patch tests, repeated at this time, were now positive. Mercaptan B was an irritant, as shown by the immediate reactions produced, but did not produce sensitization until the 12th application. Mercaptan C was not an irritant and was only a poor sensitizer under the conditions of the experiment.

COMMENT

It must be recognized that, as with the standard prophetic patch test, results obtained with this procedure may not reveal the actual percentages of persons sensitized on normal exposure. For example, users of mercaptan-containing hair-waving agents may contact the preparation only three or four times yearly, and perhaps such widely spaced exposures produce a different sensitization rate from that which results from the intensive test exposures. However, the percentages obtained in the test may be similar to those developing from normal use if this involves daily or frequent contact. Thus, of 12 technicians and others handling mercaptan A on an almost daily basis, there were 5 who became sensitized during a three-month period. In the test exposures, 5 of 16 subjects were sensitized in three weeks. In contrast, none of 40 women who had two waves at three-month intervals with this preparation showed reactions, and of 106 persons subjected to the prophetic patch test only one was apparently sensitized by it. The necessity for repeated exposures is borne out by the relatively low percentages of sensitizations obtained when the number of test applications was decreased. With one to three applications in the first week, only 1 of 15 persons was shown to be sensitized to mercaptan A in a three-week period. Mercaptans A and B are obviously potent sensitizers, and some indication of their activity was, therefore, obtained in the prophetic patch test. However, most compounds of such strong sensitizing power will reveal themselves quickly and do not require much investigation. The problem is the uncovering of allergenicity of materials in the range between mercaptan C and the two new compounds, since even such less powerfully sensitizing materials are undesirable for some uses, as in cosmetics. Experience has shown they may fail to sensitize in the Schwartz and Peck procedure.

Although, as noted, the actual sensitizing index following normal use cannot be exactly ascertained by this procedure, or any other yet devised, the method presented apparently accelerates the reaction rate and will expose allergenicity in a range outside that which is possible with the standard prophetic patch test. The method is therefore particularly adaptable for revealing the sensitizing potential of materials which will give rise to no reactions in the prophetic patch test procedure.

TREATMENT OF CONDYLOMA ACUMINATUM WITH PELTATINS

Preliminary Report

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PODOPHYLLOTOXIN [1] quercetin,[2] α-peltatin,[3] and β-peltatin [4] are crystalline compounds in podophyllin. We contended previously [5] that podophyllotoxin was the component responsible for involution of condyloma acuminatum. When α- and

TABLE 1.—*Results of Topical Treatment of Patients with Penile Condyloma Acuminatum*

	Patients							
		Cured		No. Receiving Specified No. of Treatments				
Drug *	Treated, No.	No.	%	1	2	3	4	6
α-Peltatin	21	19	90	4	9	5	2	..
β-Peltatin	11	9	81	4	5	2	..	1

* One per cent peltatin in benzoin tincture.

Read at the Seventy-Second Meeting of the American Dermatological Association, Colorado Springs, Colo., April 24, 1952.

From the United States Public Health Service Hospital, Baltimore. This work was supported by a Grant-in-Aid from the American Cancer Society.

1. (*a*) Sullivan, M.: Podophyllotoxin, Arch. Dermat. & Syph. **60**:1, 1949. (*b*) Podwyssotzki, V.: Pharmakologische Studien über Podophyllum peltatum, Arch. exper. Path. u. Pharmakol. **131**:29, 1881. (*c*) Borsche, W., and Niemann, J.: Über Podophyllin, Ber. deutsch. chem. Gesellsch. **65**:1633, 1932. (*d*) Spaeth, E.; Wessely, F., and Nadler, E.: Zur Konstitution des Podophyllotoxins und Pikro-Podophyllins, Ber. deutsch. chem. Gesellsch. **65**:1773, 1932; ibid. **66**:125, 1933.

2. (*a*) Dunstan, W. R., and Henry, T. A.: A Chemical Investigation of the Constituents of Indian and American Podophyllum (Podophyllum Emodi and Podophyllum Peltatum), J. Chem. Soc. Lond. **72**:209, 1898. (*b*) Podwyssotzki.[1b]

3. (*a*) Hartwell, J. L.: α-Peltatin, a New Compound Isolated from Podophyllum Peltatum, Correspondence, J. Am. Chem. Soc. **69**:2918, 1947. (*b*) Hartwell, J. L., and Detty, W. E.: Components of Podophyllin: III. Isolation of α- and β-Peltatin; Structure Studies, J. Am. Chem. Soc. **72**:246, 1950.

4. (*a*) Hartwell, J. L.:, and Detty, W. E.: β-Peltatin, A New Component of Podophyllin, Correspondence, J. Am. Chem. Soc. **70**:2833, 1948. (*b*) Hartwell and Detty.[3b]

5. (*a*) Sullivan, M., and King, L. S.: Effects of Resin of Podophyllum on Normal Skin, Condylomata Acuminata and Verrucae Vulgares, Arch. Dermat. & Syph. **56**:30, 1947. (*b*) Sullivan, M.; Freidman, M., and Hearin, J. T.: Treatment of Condylomata Acuminata with Podophyllotoxin, South. M. J. **41**:336, 1948. (*c*) Sullivan.[1a]

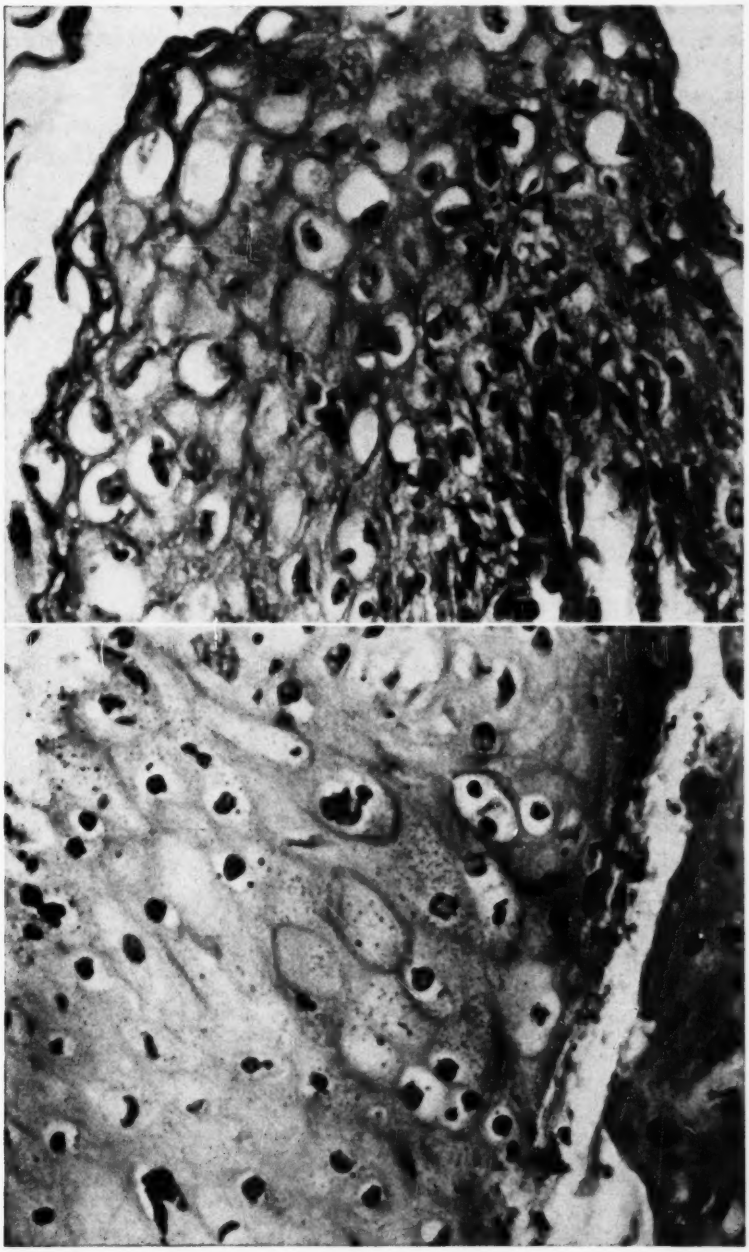

Fig. 1.—Condyloma acuminatum 24 hours after application of 1% α-peltatin in tincture of benzoin; swollen epidermal cells with accentuated cell outlines, spongy cytoplasm, perinuclear vacuolation, pyknosis, disintegration and disappearance of nuclei, dispersion of keratohyaline granules, and vacuolation of entire cells; × 500.

β-peltatin became available,[6] 32 patients were treated (Table 1). Satisfactory results necessitate including these substances as effective agents against moist genital warts. The clinical response to the topically applied peltatins was identical with that described in detail for podophyllin and podophyllotoxin[7] except that the peltatins produced negligible irritation to circumjacent normal tissue. Microscopic examination of involuting warts at 24 and 48 hours showed changes[7] identical with those

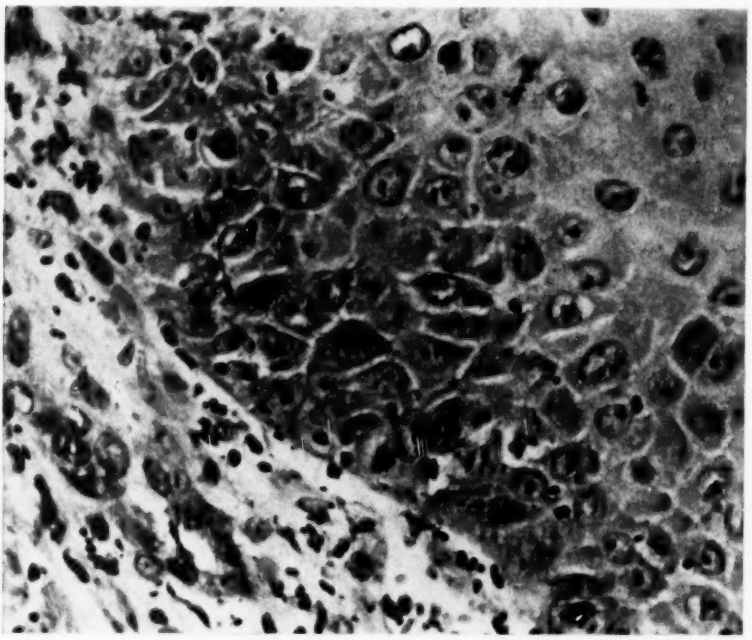

Fig. 2 (same preparation as in Fig. 1).—Arrest of mitoses in cells near basal layer ("podophyllin cells"); × 500.

TABLE 2.—*Results of Patch Tests with Peltatins*

Drug *	Amount	Patients, No.	Positive Reactions	
			No.	%
α-Peltatin	0.05 cc.	108	1	0.9
β-Peltatin	0.05 cc.	108	1	0.9

* One per cent in benzoin tincture.

6. The peltatins used in this study were supplied by Dr. M. J. Shear, National Cancer Institute, Bethesda, Md.

7. (*a*) King, L. S., and Sullivan, M.: Effects of Podophyllin and Colchicine on Normal Skin, on Condyloma Acuminatum and on Verruca Vulgaris: Pathologic Observations, Arch. Path. **43**:374, 1947. (*b*) Sullivan and King.[5a] (*c*) Sullivan.[1a]

produced by podophyllotoxin. Patch tests (Table 2) indicated a low sensitizing index; by similar technique podophyllotoxin produced 8% positive reactions.[1a] When podophyllotoxin is dissolved in alkaline solutions, it is converted to picropodophyllin and podophyllic acid, which are ineffective against condyloma acuminatum [8]; the peltatins possess the advantage that they may be dissolved in caustic bases [8] and utilized for treating cornified verrucae.

8. (*a*) Leiter, J.; Downing, V.; Hartwell, J. L., and Shear, M. J.: Damage Induced in Sarcoma 37 with Podophyllin, Podophyllotoxin Alpha-Peltatin, Beta-Peltatin and Quercetin, J. Nat. Cancer Inst. **10**:1273, 1950. (*b*) Hartwell and Detty.[3b]

INFLAMMATORY CARCINOMA OF THE BREAST

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ALTHOUGH inflammatory carcinoma of the breast is an entity well known to surgeons, it is comparatively uncommon, comprising only about 1 to 4% of all breast carcinomas. Since it clinically simulates an inflammatory process, it frequently is difficult to diagnose. In 14 (18.9%) of the 74 cases seen at the Mayo Clinic between 1933 and 1945,[1] the condition was erroneously diagnosed "inflammatory disease" before the true carcinomatous nature was discovered. When full-blown it resembles erysipelas, and dermatologists may be consulted for diagnosis and treatment. The condition is only briefly mentioned in the dermatologic texts, and in the American dermatologic literature there is but one report of inflammatory, or erysipeloid, breast carcinoma. Leavell and Tillotson [2] in a recent issue of the A. M. A. ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY report the case of a woman who died of a breast carcinoma exhibiting three types of metastatic skin lesions, namely, inflammatory carcinoma, carcinoma telangiectaticum, and nodular carcinoma. Freeman and Lynch [3] have reported a case of carcinoma of the breast which presented telangiectatic and cystic lesions superimposed upon an infiltrated skin. These authors believed that the neoplasm in their case was a form of subepidermal carcinoma, wherein the cancer cells spread chiefly through blood vessels.

The diagnosis of inflammatory breast malignancy can become especially difficult when the first manifestation is a nondescript dermatologic lesion in the form of a "scaly, red spot" on the side of the neck at some distance from the involved breast.

REPORT OF A CASE

O. N., a 52-year-old somewhat obese white woman, was admitted to the hospital on July 23, 1951, complaining of weakness, anorexia, and an extensive painful eruption involving the left breast, the neck anteriorly and posteriorly, and the left shoulder and adjacent upper left thorax. The lesion began approximately three months previously as a "round, red spot" on the left side of the neck near the shoulder. This spot "became larger," but she did not seek treatment until the early part of June. The first physician consulted prescribed a simple ointment, but the redness began to spread over the shoulder toward the back and anteriorly over the left breast. On June 15 a second physician began to treat her for erysipelas with large doses of penicillin. The pendulous portion of the breast at this time was not yet involved. Obtaining no relief, the patient sought help from a cultist. The disorder soon involved the entire left breast, which

From the Dermatology Division, Medical Service, Sacred Heart Hospital.

1. Meyer, A. C.; Dockerty, M. B., and Harrington, S. W.: Inflammatory Carcinoma of the Breast, Surg. Gynec. & Obst. **87**:417-424 (Oct.) 1948.

2. Leavell, U. W., and Tillotson, F. W.: Metastatic Cutaneous Carcinoma from the Breast, A. M. A. Arch. Dermat. & Syph. **64**:774-782 (Dec.) 1951.

3. Freeman, C. D., and Lynch, F. W.: Carcinoma of the Breast with Peculiar Cutaneous Metastases, Arch. Dermat. & Syph. **35**:643-652 (April) 1937.

became red, swollen, and painful. A third physician administered sulfonamides, more penicillin, streptomycin, and chloromycetin, all without benefit. The patient became weak, lost her appetite, and was unable to lift her left arm or move her neck without considerable pain.

The past personal and family histories were essentially noncontributory. The patient generally had enjoyed good health until the onset of her present condition, early in May, 1951. For about a month after the symptoms began, she continued to work. There was no history of trauma.

The physical examination revealed a 52-year-old white woman, appearing quite ill, lying restlessly in bed, and complaining of pain in the region of the neck and left shoulder. Examination of the head showed nothing abnormal. On the neck, the skin, particularly on the left side, was extremely thickened and tense. Cervical nodes were not palpable. The heart, lungs, and abdomen were normal. The blood pressure was 180/20. The abdomen was obese, and the

Fig. 1.—Appearance of breast approximately three months after onset of symptoms.

skin presented striae of a silvery nature, due to either obesity or previous pregnancy. No organs or masses were palpable. The skin disorder involved the left shoulder, left upper extremity, and back principally. There was marked limitation of motion of the left upper extremity due to pain.

There was an extensive, confluent, dusky erythematous, indurated, nodular, board-like eruption involving the neck anteriorly and posteriorly, the left shoulder, left clavicular area, upper left thorax, and entire left breast, which was markedly edematous and exhibited a brawny induration. The entire eruption was well demarcated and arranged in a segmental fashion, terminating at the top of the left shoulder in a vest-like manner. The involved skin was hot to the touch and firmly attached to the underlying structures. The left breast was uniformly enlarged—probably one-third larger than the right breast. No definite mass could be palpated. Some oozing and exfoliation were present over the upper left thorax and nuchal areas

The provisional diagnoses were (1) phlegmon (cellulitis), and (2) possible erysipeloid carcinoma of the breast.

Results of urinalysis and a complete blood cell count were all within normal limits. The corrected sedimentation rate was 55 mm. in one hour; the blood sugar was 78 mg. per 100 cc. A serologic test for syphilis was negative. Blood culture revealed no growth in 48 hours.

A surgical consultant saw the patient and ruled out carcinoma because no definite mass was palpable in the breast and because of the wide extent of the involved area. He was also influenced by the fact that the original lesion was on the left side of the neck, spreading to the breast secondarily. It was his impression that the condition was a diffuse, extensive, inflammatory lymphangitis of undetermined origin. A biopsy was recommended for cultural studies mainly.

Roentgen examination of the chest revealed a moderate-sized, ovoid density, paralleling the right lateral chest wall. There was no significant change in size and configuration in films taken in the erect and the recumbent position, and, although a loculated pleural effusion could

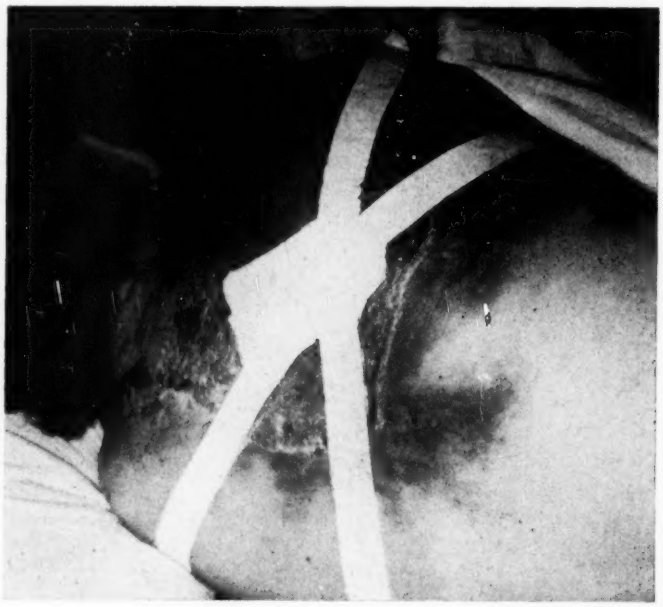

Fig. 2.—Skin of upper left thorax and site of biopsy.

have caused such an appearance, the picture was probably one of pleural thickening "possibly because of tumor formation."

The patient's temperature fluctuated between 99 and 102 F. After her admission to the hospital, the eruption gradually became worse, spreading to the entire neck, which she was unable to move without considerable discomfort. The patient was in constant pain, obtaining very little relief from large doses of meperidine (demerol®) hydrochloride and barbiturates. Anorexia and vomiting became severe. She was given daily transfusions of whole blood, and after the diagnosis was established deep roentgen therapy was administered daily to various areas of the tumor. After this, the left upper extremity became edematous, particularly the left hand, and the disease process began to spread to the sternum and right breast. She became progressively worse and died suddenly on the 16th day of hospitalization. An autopsy was not permitted.

Report of Biopsy.—The sections of the skin from the back showed groups of malignant cells which were largely seen to be within the dermis. In some instances, these cells appeared to be

in the lymphatics of the skin, as there was a definite endothelium about them; however, in other instances, the malignant groups of cells were within the fibrous stroma. In the perivascular lymphatics of the subcutaneous tissue were seen groups of malignant cells. The malignant cells were irregular, being cuboidal, oval, and of a spindle-cell type, having an irregular vesicular nucleus showing a moderate degree of mitosis. The dermis showed a diffuse infiltration of chronic inflammatory cells consisting mainly of lymphocytes and a few plasma cells. There were groups of polymorphonuclear leucocytes and an occasional eosinophile also was seen in the dermis. The collagenous tissue of the dermis was fragmented, with a large degree of edema.

The diagnosis was inflammatory carcinoma in the skin with its origin most likely from the breast.

COMMENT

The fact that the presenting sign began as an inflammatory area on the left side of the neck with apparent secondary involvement of the breast makes this case particularly interesting, especially to dermatologists. Surgeons occasionally encounter enlarged axillary lymph nodes in which the pathologist finds secondary metastatic carcinoma, the focus being a lesion in the breast the size of a pea or smaller. The vagary of the lymphatic spread of malignant cells is, undoubtedly, thus exhibited in our case.

Reuter and Nomland [4] reported inflammatory carcinoma of the skin secondary to carcinoma in organs other than the breast. They describe an extensive, erysipelas-like eruption that was present on the face and neck of a 60-year-old man. The biopsy revealed diffuse invasion of all levels of the cutis by strands of carcinoma cells. The patient later admitted rectal trouble, and a record, two years old, was found in which a diagnosis of carcinoma of the rectum was made.

Harvey and Cochrane [5] describe a case of inflammatory carcinoma which was diagnosed as carcinoma *en cuirasse*. The patient was treated for about three months for a chronic streptococcic infection of the chest wall. The authors believed the condition to be metastatic from a carcinoma of the stomach.

The neoplasm in the case presented here falls into the variety of inflammatory carcinoma of the breast which Taylor and Meltzer [6] describe as "primary." These authors designate this group as the one in which the signs of inflammation arise simultaneously with carcinoma in a previously normal breast. The "secondary" inflammatory carcinoma is the type in which the inflammatory symptoms occur suddenly in a breast which has been the seat of a scirrhous carcinoma or follow a mastectomy or development of a malignant tumor in the opposite breast. The secondary type is identical with carcinoma *en cuirasse* and offers no diagnostic difficulty in the majority of cases. In the primary type, however, as previously stated, the erroneous diagnosis of erysipelas or cellulitis is frequently made and the condition tragically treated as such. Granted we are dealing with a very virulent type of cancer, if the true nature of the disorder could be recognized early the insti-

4. Reuter, M. J., and Nomland, R.: Inflammatory Cutaneous Metastatic Carcinoma, Wisconsin M. J. **40**:196-201 (March) 1941.

5. Harvey, G., and Cochrane, T.: Carcinoma en Cuirasse: Primary Lesion in Stomach, Arch. Dermat. & Syph. **62**:651-654 (Nov.) 1950.

6. Taylor, G. W., and Meltzer, A.: "Inflammatory Carcinoma" of the Breast, Am. J. Cancer **33**:33-49 (May) 1938.

tution of surgery, irradiation, or both would prolong the lives of some of these persons. One must certainly endorse the statement of Taylor and Meltzer [6] that inflammatory signs developing in the skin on or about the breast which do not subside within two or three weeks warrant a biopsy for diagnosis.

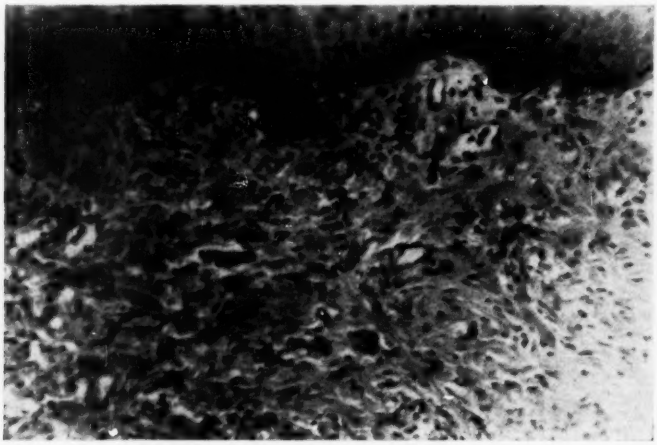

Fig. 3.—Malignant cells in dermal lymphatics; × 80.

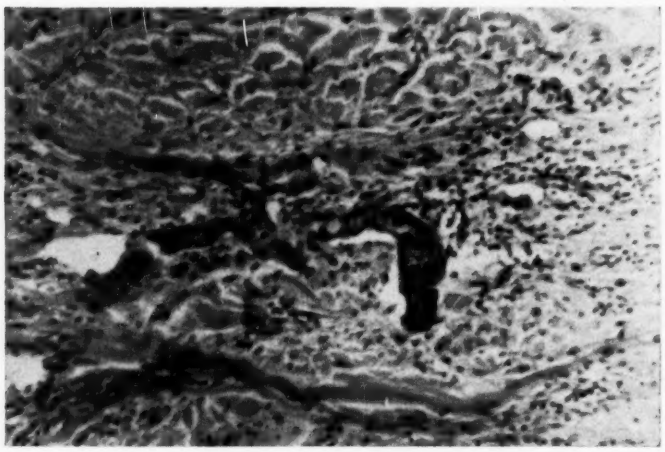

Fig. 4.—Same as Figure 3; × 100.

PATHOLOGY

The pathologic picture was quite typical for inflammatory breast carcinoma. All the lymphatic vessels, the deeper ones in the fatty layer as well as the subepidermal lymphatics at the level of the sweat glands, were filled with cancer cells. The plugged lymphatics were in such close proximity to the sweat glands that sweat duct carcinoma was suggested in some areas. The histologic picture was somewhat

unusual in the large amount of fibrosis that was exhibited. This fibrosis, of course, was manifested clinically by the board-like sclerodermatous consistency of the involved areas. No evidence of infection was present, but lymphocytes were abundant. This accompanying lymphocytic reaction is believed by some to be due to an

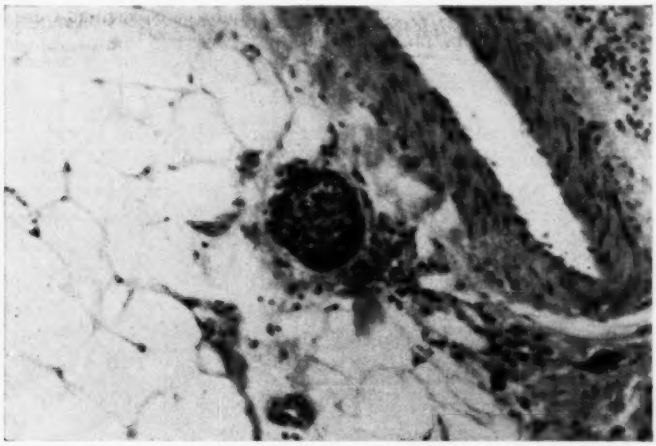

Fig. 5.—Malignant cells in perivascular lymphatics; × 80.

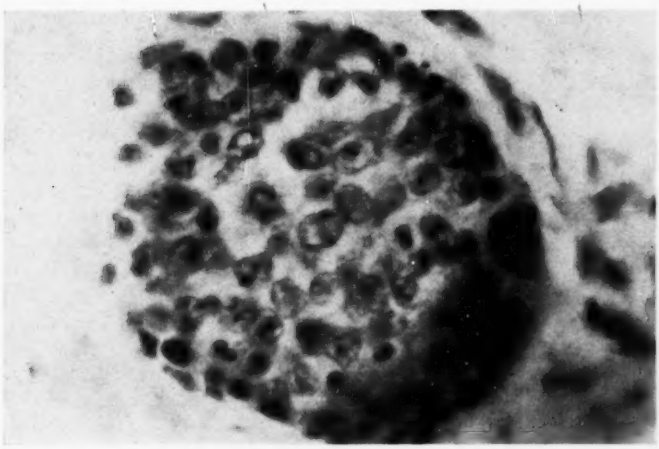

Fig. 6.—Same as Figure 5; × 400.

irritant product of the carcinoma, while others believe it is due to the blockage of lymphatics which prevents reentry of cells into the vessels. Capillary congestion is responsible for the erythema and heat, while the widespread lymphatic blockage prevents drainage and causes edema.

Through the courtesy of Dr. Herman Beerman, the case was presented in December, 1951, at the meeting of the American Academy of Dermatology and

Syphilology before the panel demonstration in histopathology. In the discussion which followed, Dr. Reuben Nomland stated that in some cases of inflammatory carcinoma in which the lymphatics in the upper corium only are blocked with tumor cells the inflammatory symptoms may peculiarly clear with simple compresses. However, when the deeper lymphatics are plugged and when there is diffuse invasion of the lower cutis by strands of carcinoma cells, such as were exhibited in our case, the inflammatory phenomena do not clear and the prognosis is especially grave.

SUMMARY

An unusual case of primary inflammatory carcinoma of the breast is described in which the first manifestation was a solitary red area on the side of the neck with subsequent involvement of the breast on the same side. The condition was erroneously diagnosed and treated as erysipelas for approximately three months before the true diagnosis was established.

ACNE NEONATORUM

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LIEUTENANT COMMANDER WILLIAM K. HALL (MC), U. S. N.
AND
MAURICE M. TOLMAN, M.D.
CHELSEA, MASS.

THE ORIGINAL report of acne neonatorum was that of Kraus in 1913. He maintained that many cases previously diagnosed as sebaceous milia in infants were actually acne vulgaris. His views were supported by pathological studies, and illustrations from two cases were presented.[1] The next case was that of Beatty and Bigger in 1923.[2] They thought that the diagnosis was established by obtaining positive cultures for the acne bacillus and Staphylococcus aureus from the lesions. Since then, 14 additional cases have been reported. Unfortunately, many of the case reports are incomplete and therefore inadequate for full evaluation. Only a few are documented by photographs. These case reports[3] are summarized in Table 1.

Certain conclusions may be drawn from Table 1. The disease favors the male sex; in 12 reported cases the patients were boys and in only 5 were they girls. Comedones were present in all cases, and papules and pustules were present in most cases. In one instance each, cystic lesions[3e] and deep-seated nodules[3d] were present. The distribution was constant. The cheeks were usually, and occasionally the only sites, involved. The chin and forehead were the next commonest sites of involvement. In no instances were lesions noted on any area but the face.

The age at onset was difficult to ascertain, as was the duration of the disease in some cases. The more detailed the reports, the younger the age at onset appeared to be. In some instances erythema, dryness, papules, or milia were noticed very

From the United States Naval Hospital.

This article has been released for publication by the Division of Publications of the United States Navy. The opinions and views set forth in this article are those of the writers and are not to be construed as reflecting the policies of the Navy Department.

1. Kraus, A.: Über Akne neonatorum, Arch. Dermat. u. Syph. **116**:704, 1913.

2. Beatty, W., and Bigger, J. W.: Acne in an Infant, Brit. J. Dermat. **35**:325 (Aug.-Sept.) 1923.

3. (*a*) Kraus.[1] (*b*) Beatty and Bigger.[2] (*c*) Ayres, S., Jr.: Infantile Acne Vulgaris, Arch. Dermat. & Syph. **14**:12 (July) 1926. (*d*) Gray, A. M. H.: Acne in a Child Aged 2 Years, Proc. Roy. Soc. Med. **27**:292 (Nov. 16) 1933. (*e*) Belisario, J. C.: Acne Vulgaris in Infant, M. J. Australia **1**:116 (Jan. 21) 1939. (*f*) Aitken, R.: Acne Vulgaris in Infants, Brit. J. Dermat. **54**:272 (Oct.) 1942. (*g*) Slavens, J. J.: Infantile Acne Vulgaris, J. Pediat. **20**:365 (March) 1942. (*h*) Perlman, H. H.: Acne Neonatorum: Report of Acne Vulgaris in 2 Infants, J. Pediat. **33**:609 (Nov.) 1948.

shortly after birth, with comedones and secondary lesions appearing within weeks to months thereafter. In most instances the typical lesions were noted by the third month. In those cases which were followed until remission occurred, the duration was usually less than eight months, pitted scars being the only residua.[3g,h] The therapy was invariably conservative.

In the earlier reports the authors apparently considered bacterial infection a prime etiologic factor and concerned themselves with demonstration of the acne bacillus.[3d,h] A hormonal factor is more frequently considered at present [3e,h]; however, in only one case was there evidence suggestive of endocrinopathy.[3h] Local

TABLE 1.—*Reported Cases of Acne Neonatorum*

Case	Author	Date	Sex	Age at Onset	Lesions and Distribution
1	Kraus [1]	1913	F	Under 3 mo.	Comedones on forehead, cheeks, and chin
2	Kraus [1]	1913	M	Under 2 mo.	Comedones on forehead and cheeks
3	Beatty and Bigger [2]	1923	M	Under 3 mo.	Papules, papulopustules, and few comedones on cheeks; comedones on chin
4	Ayres [3c]	1926	M	20 mo.	Comedones, papules, and pustules confined to chin
5	Ayres [3c]	1926	M	3 mo.	Comedones, papules, and pustules on cheeks and chin
6	Ayres [3c]	1926	M	8 wk.	Comedones on chin and nose; few papules and pustules
7	Gray [3d]	1934	F	Seen at 2 yr.	Comedones, papules, and deep-seated nodules limited to cheeks
8	Belisario [3e]	1939	M	3 mo.	Cystic lesions, papules, and comedones around mouth and on cheeks
9	Aitken [3f]	1942	M	7 mo.	Comedones on cheeks and chin
10	Aitken [3f]	1942	F	11 mo.	Comedones, pustules, and scars on both cheeks
11	Aitken [3f]	1942	F	10 mo.	Comedones and pustules on both cheeks
12	Aitken [3f]	1942	M	2½ mo.	Comedones and pustules on both cheeks
13	Aitken [3f]	1942	M	2 wk.	Comedones, papules, and pustules on both cheeks
14	Slavens [3g]	1942	M	Under 3 mo.	Comedones, papules, and pustules on cheeks; residual of pitted scars
15	Slavens [3g]	1942	M	1 mo.	Comedones and pustules on cheeks; residual of pitted scars
16	Perlman [3h]	1948	M	1 wk. (?)	Milia on forehead and cheeks followed by pustules and comedones on forehead and face
17	Perlman [3h]	1948	F	1 mo.	Papules and comedones on forehead, cheeks, and chin

factors, such as the use of oil on the face, have been suggested as a cause,[3d,g] but the reports are not convincing.

In the older literature the condition known as "grouped comedones" was reported. "Grouped comedones" in infants and children were first described by Crocker in 1884.[4] It has been said [5] that the comedones of this condition differ from those of acne vulgaris in being smaller, in being more closely set, in showing no tendency toward inflammation or suppuration, and in frequently being caused by a local irritant.

However, not all 12 cases of this condition which we were able to find in the literature fulfilled these criteria. The 12 cases [6] are summarized in Table 2.

4. Crocker, H. R.: Comedones in Children, Lancet **1**:704 (April 19) 1884.

5. Adamson, H. G.: The Skin Affections of Childhood: With Special Reference to Those of More Common Occurrence, and Their Diagnosis and Treatment, London, H. Frowde, 1907, pp. 56-57.

(Footnotes continued on next page)

Of these cases, in two (Cases 1 and 10) the condition occurred in older children; and in three (Cases 4, 7, and 12) it seemed the direct result of prolonged use of camphorated oil. In the other seven cases the patients were infants. There was no obvious irritant present. The lesions were invariably limited to the cheeks, chin, and forehead. All seven were boys.

Thus it is seen that these seven cases (Cases 2, 3, 5, 6, 8, 9, and 11) agree in age, sex, distribution, and lesions with the cases of acne neonatorum, with which they are probably identical. If they are actually instances of acne neonatorum, they increase the number of reported cases of that condition to 24.

"Grouped comedones" have not been reported since 1918. Possibly this lack of case reports parallels the improvement of hygiene in the general populace or results from progress in infant care. It also seems likely that many cases previously

TABLE 2.—*Reported Cases of "Grouped Comedones" in Children*

Case	Author	Date	Sex	Age at Onset	Lesions and Distribution
1	Crocker [4]	1884	M	Seen at 3½ yr.	Comedones grouped on right forehead and occipital area
2	Crocker [4]	1884	M	9 mo.	Grouped comedones on cheeks
3	Crocker [4]	1884	M	8 mo.	Grouped comedones on cheeks
4	MacLeod [6b]	1905	M	Under 2 yr.	Grouped comedones and acneiform lesions over sternum, about nipples and umbilicus in area treated with camphorated oil
5	MacLeod [6b]	1905	M	Under 1 yr.	Grouped comedones on forehead and cheeks
6	MacLeod [6c]	1907	M	4 mo.	Comedones on cheeks and chin
7	Dore [6d]	1909	M	1 yr.	Indurated follicular lesions with large comedones on cheeks and abdomen; history of application of camphorated oil
8	Harries [6e]	1911	M	Seen at 6 mo.	Closely set comedones on both cheeks
9	Harries [6e]	1911	M	Seen at 9 mo.	Comedones on cheeks and forehead
10	Harries [6e]	1911	M	Seen at 3½ yr.	Comedones on malar prominences and forehead
11	Harries [6e]	1911	M	1 mo.	Comedones on cheek, chin, and forehead; few pustules
12	MacLeod [6f]	1918	?	Infant	Grouped comedones on neck and upper chest with occasional pustules in area anointed with camphorated oil

reported as instances of "grouped comedones" are in reality cases of acne neonatorum—perhaps of a mild degree—and are now so recognized and reported.

REPORT OF A CASE

S. B., a white boy, born on Sept. 12, 1951, was referred to the skin clinic by the pediatrics department because of an eruption on the cheeks and chin first noted at the age of 18 days.

Both maternal and paternal family histories were negative for endocrine, allergic, infectious, neoplastic, or dermatologic disease patterns.

The father, aged 27 years, has always enjoyed good health. He had only the usual diseases of childhood and these without complication. Save for "adolescent pimples," his skin has been and now is clear.

The mother is a healthy, 25-year-old woman, primipara and primigravida. She had the usual childhood diseases and scarlatina without sequelae. The menarche occurred at 13 years.

6. (*a*) Crocker.[4] (*b*) MacLeod, J. M. H.: Case Presentation, Brit. J. Dermat. **17**:141 (April) 1905; (*c*) Case Presentation, ibid. **19**:424 (Dec.) 1907. (*d*) Dore, S. E.: Case Presentation, ibid. **21**:220 (July) 1909. (*e*) Harries, E. H. R.: A Note on Some Cases of Grouped Comedones in Infants, ibid. **23**:5 (Jan.) 1911. (*f*) MacLeod, J. M. H.: Case Presentation, ibid. **30**:181 (July-Sept.) 1918.

Her periods were at first associated with syncope and cramps, necessitating "injections," but have since been regular and without significant dysmenorrhea.

Conception occurred without difficulty. During the first five months of pregnancy considerable nausea and emesis were experienced; despite this, however, she pursued her usual occupation as a stenographer. Her family physician advised her to eat "a lot of sweets." This she did, but only a moderate amount of the intake was in the form of chocolate. Iodized salt was used and had been a standard household item for as long as she could recall. Hormones and sedatives, such as bromides, were not prescribed or taken during the pregnancy.

Results of routine examinations during the pregnancy were negative. There was no vaginal bleeding. At no time were acneform lesions present. Urinalyses, hematological studies, a serological test for syphilis, and an x-ray of the chest disclosed no abnormalities.

After an uneventful labor, spontaneous delivery was accomplished under saddle (procaine) block. Premedication was with amobarbital (amytal), meperidine (demerol®) hydrochloride, and scopolamine hydrobromide. The placenta was normal. Postpartum medication consisted of ergonovine maleate and ferrous sulfate, and her course was without event.

Acne neonatorum.

The infant weighed 5 lb. 15 oz. (2,240 gm.) at birth and presented no physical abnormalities. Silver nitrate was instilled into the conjuctival sacs at birth. Circumcision was performed on Sept. 15, 1951. Thimerosal (merthiolate®) was used as the antiseptic, and an ammoniated mercury dressing was applied.

The infant was breast-fed for but one week. Then with the failure to gain weight a formula consisting of evaporated milk and corn syrup, and later granulated sugar, was substituted. At 5 weeks of age a cereal was added to the diet, and at 10 weeks of age fruits and vegetables were included.

For the first two weeks of life the skin was cleansed with baby oil. About Oct. 1 the mother noted an erythematous papulopustular eruption on both cheeks and chin. Within 7 to 10 days she also noted the presence of many "blackheads." The family physician was consulted and the following therapeutic agents were prescribed in sequence: "Mazon" ointment (containing mercury salicylate, benzoic acid, salicylic acid, and tars) was used for 4 days (Oct. 4 to 8), followed by aureomycin ointment for 10 days (Oct. 8 to 18). Later ultraviolet light therapy was utilized for 3 days (Oct. 22 to 25), and finally an injection of 300,000 units of penicillin was given (Oct. 25). For 10 days before the initial visit to the clinic only baby oil was applied locally (Oct. 25 to Nov. 5).

The infant was first seen by us on Nov. 6. At that time many comedones, papules, and pustules were present on the cheeks, chin, and forehead. There was a moderate seborrhea capitis. The skin of the rest of the body was clear.

The infant's general health and development have been considered normal by the pediatricians. At no time was breast or genital enlargement noted. There has been no evidence of endocrinopathy. Findings on x-ray examination of the skull were normal.

Treatment consisted of application of mild drying shake lotions. By March 1, 1952 (five months after the onset of the eruption), the pustules and papules had subsided. Erythema and slight scaling persisted on the cheeks. A few comedones remained on the chin. There was one pit on the nose.

COMMENT

This case is believed to be consistent with the diagnosis of acne neonatorum. The sex, lesions, and distribution appear to be quite typical of the disease. No definite etiologic factors were apparent. The mother's use of iodized salt and the use of oils in neonatal life are not believed to be significant. No evidence of endocrinopathy was present, and there was no reason to suspect adenoma sebaceum. The hygiene was faultless, and evidence of intrinsic or extrinsic bacterial contamination was lacking. The simultaneous presence of seborrhea capitis is of interest.

We are of the opinion that acne neonatorum is acne vulgaris in infants. It differs from acne in adolescents, however, in that merely the face is affected, never the back or chest. Since most of the factors which are usually considered important in the causation of acne in adolescents, such as various food factors, lack of hygiene, constipation, etc., are not present in the infant, it would seem that acne in infants is most likely due to some hormonal factor. The same assumption may be drawn from the fact that in 13 of 18 reported cases the patients were male.

SUMMARY

The available literature on acne neonatorum and "grouped comedones" in infants and children has been reviewed.

We believe that acne neonatorum is acne vulgaris occurring in infants.

We are of the opinion that some cases previously reported as instances of "grouped comedones" in infants in whom no local irritant was obvious were in reality cases of a less severe form of acne neonatorum.

A case of acne neonatorum with onset of typical lesions at the age of 4 weeks is presented. The sex, distribution, and morphology of the lesions are similar to those noted in previously reported cases.

ALOPECIA AREATA, ACNE, AND MILIA

Report of a Unique Case Illustrating the Importance of Hair as a Natural Drain

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BERKELEY, CALIF.
AND
CAPTAIN GORDON H. EKBLAD (MC), U. S. N.

THE PRIMARY lesion of acne vulgaris is generally conceded to be the comedo. In all probability there are multiple factors which play a part in the formation of this anatomical defect and its close relative, the milium. It has long been speculated by Sulzberger, and reported by him and his associates, Witten [1] and Berger [2] that

> it is possible that in modern man the lanugo hair may represent a vestigial and disappearing organ no longer capable of doing the job of its coarse and thicker predecessor in holding open the follicular orifices. The failure of certain of the feeble lanugo hairs to keep patent the opening of the follicle and to maintain adequate drainage of sebum would seem to be sufficient to account for the comedones which appear in susceptible persons at puberty or in later years.[1]

We consider that excellent evidence for the soundness of this hypothesis is furnished by the following case summary and photographs of a patient with alopecia areata presenting typical lesions of acne vulgaris, cystic acne, and milia, which developed only in areas of hair loss.

REPORT OF CASE

J. D. D., a white boatswain's mate, aged 30, was first seen by us on June 23, 1950. Multiple areas of hair loss involving the face, scalp, neck, extremities, and trunk had developed approximately two years prior to our first examination. There had been no known associated physical or mental disease. The alopecia had persisted without evidence of regrowth of hair. Shortly after the alopecia appeared, the other lesions began developing in some of the areas of alopecia. The patient's general health had been good.

On physical examination, no abnormalities were discovered except those involving the skin. The patient was a moderately hairy robust white man. There were multiple, sharply marginated areas of complete alopecia fairly symmetrically disposed over the face, neck, occipital portion of the scalp, trunk, and extremities (Figs. 1 and 2). These areas were approximately palm-sized

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This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth are those of the writers and are not to be construed as reflecting the policies of the Navy Department.

1. Sulzberger, M. B., and Witten, V. H.: Symposium on Diseases of the Skin: Hormones and Acne Vulgaris, M. Clin. North America **35**:373 (March) 1951.

2. Sulzberger, M. B., and Berger, S. S.: General Remarks on the Management of Skin Diseases with Special Reference to Acne Vulgaris, Bull. M. Soc. County of Kings **28**: (March) 1949.

Fig. 1.—Front and back views showing extensive areas of alopecia areata with secondary acne lesions in some of them.

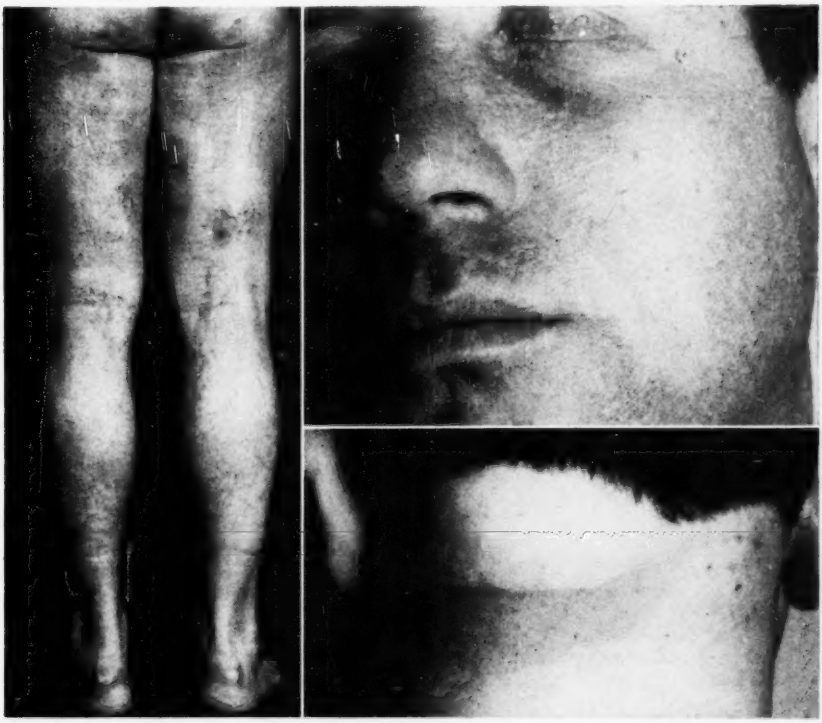

Fig. 2.—Areas of alopecia areata, some with secondary milia and some with secondary acne lesions.

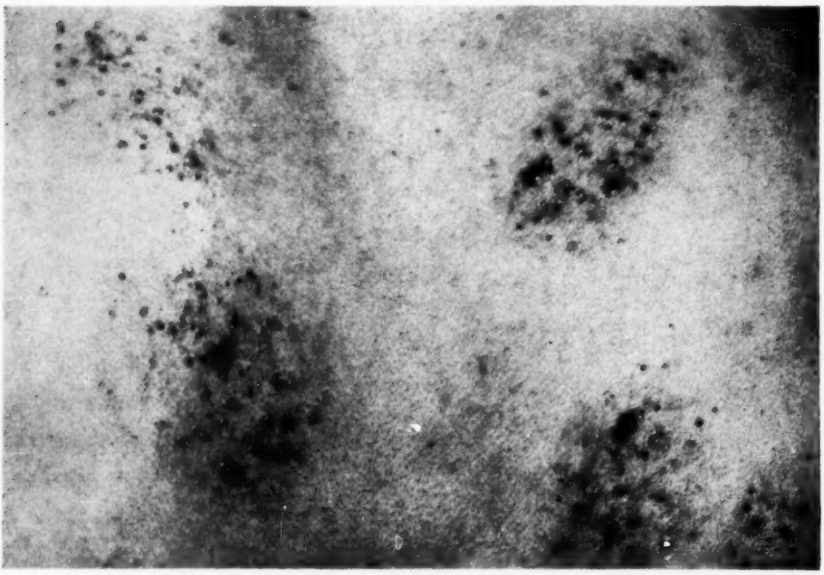

Fig. 3.—Close-up of back showing comedones and pustules of acne in areas of alopecia areata.

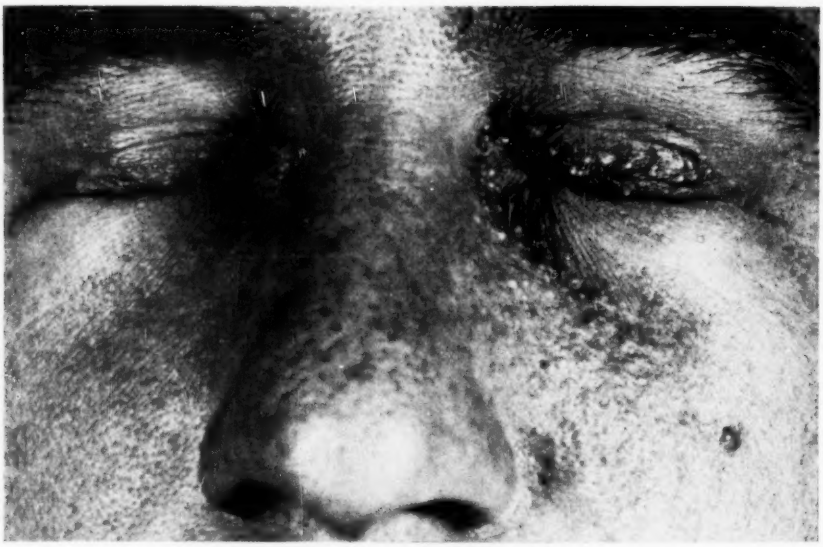

Fig. 4.—Milia and comedones in areas of loss of lanugo hair in alopecia areata.

Fig. 5.—Section from cheek showing cystic acneform lesions; × 26.

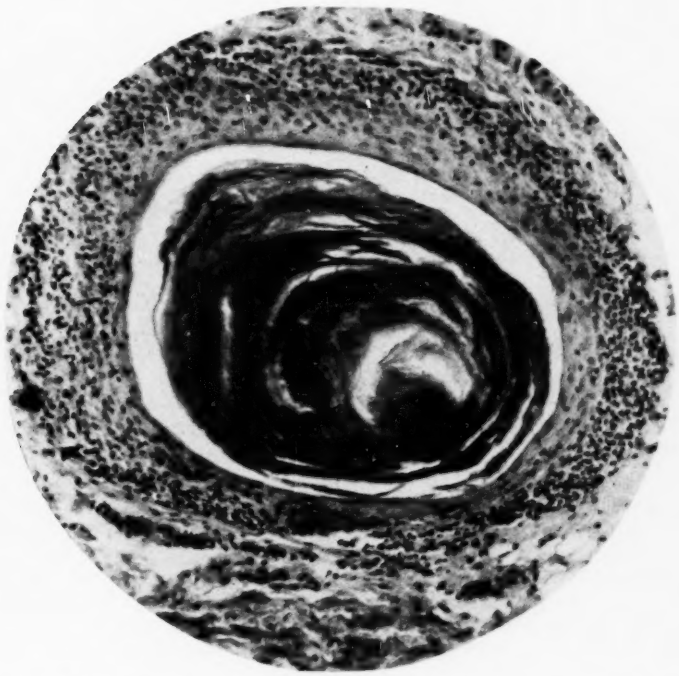

Fig. 6.—Higher-power view of cystic lesion in lower right hand corner of 5; × 145.

over the trunk and lower extremities but were smaller on the upper extremities, occiput, upper and lower eyelids, face, and neck. Within many of the areas of alopecia, but not in all, were numerous flesh-colored papules, each surmounted by a tiny glandular orifice, many black comedones, and a few pustules (Fig. 3). On the eyelids and adjacent skin were numerous typical milia (Fig. 4).

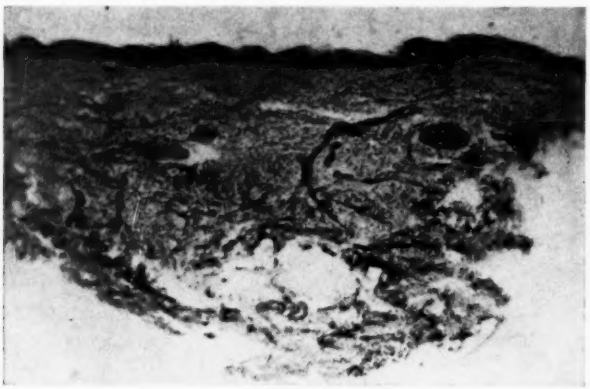

Fig. 7.—Section of alopecia areata without acneform lesions showing complete absence of pilosebaceous apparatus; × 26.

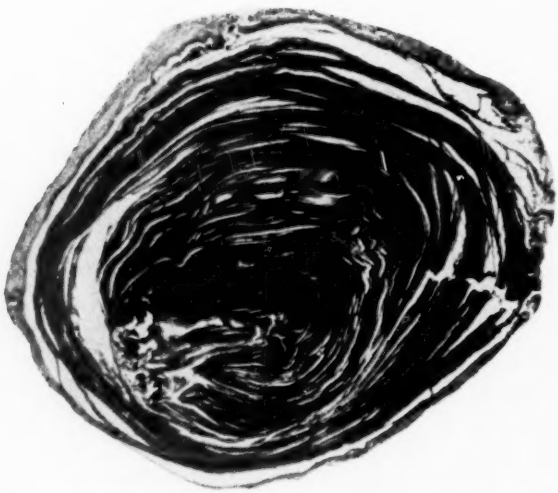

Fig. 8.—Section from milium of eyelid showing an epithelial cyst; × 49.

Findings on laboratory examinations, including blood Kahn test, complete blood cell count, and urinalysis, were within normal limits. The basal metabolic rate was + 9% on one occasion and + 21% on another. An x-ray of the chest was normal.

Histopathological studies were made from multiple areas. A section from one cheek in an area clinically showing alopecia and comedones microscopically showed prominent epithelial cysts in the corium, surrounded by a prominent chronic inflammatory infiltrate (Figs. 5 and 6). The epithelial lining of the cysts was atrophic. An atrophic hair follicle with atrophic

sebaceous glands was seen. The epidermis showed multiple areas of loss of pigment in the basal cell layer, and there was a marked increase in the melanin in the chromatophores in the upper corium. There was a mild perivascular chronic inflammatory infiltrate. A similar pathological picture was seen in a biopsy specimen taken from a leg area, clinically the same as the cheek area. In addition, one degenerated cyst surrounded by foreign body giant cells was seen in this section.

A section from the lower extremity, (Fig. 7) from an area clinically showing alopecia but no other lesions, microscopically revealed complete absence of hair follicles, but preservation of the sweat glands, and a mild perivascular chronic inflammatory type of infiltrate.

A section (Fig. 8) from a milium of the eyelid showed an epithelial cyst.

A section from an area of alopecia of the scalp, clinically without other lesions, showed complete absence of hair follicles microscopically.

Therapy, consisting of 200,000 units of water-dispersible vitamin A daily over a period of two months, was without benefit. Treatment of the comedones and cysts by the method of Nomland[3] (monoterminal electrodesiccation) gave a satisfactory result so far as these lesions were concerned. There was no regrowth of hair.

COMMENT

This interesting case illustrated the following significant points: 1. Acne of the vulgaris and cystic types appeared in a white man subsequent to the development of an extensive alopecia areata. 2. Comedones, cysts, and milia occurred only in areas of alopecia. 3. No comedones, cysts, or milia developed in areas of alopecia where microscopic sections showed complete degeneration of the pilosebaceous apparatus or in areas where there was normal hair growth. 4. The loss of the hair, which keeps open the orifice of exit for materials elaborated within the pilosebaceous apparatus, would therefore seem to be responsible for the development of the comedones, acne cysts, and milia, providing that the pilosebaceous apparatus itself is not completely destroyed.

In this case we have seen the development of cysts, comedones, and milia due to the loss of hair occasioned by alopecia areata. Such loss or absence of hair, from whatever cause, might well explain the formation not only of the primary lesion of acne but also of many sebaceous cysts, epithelial cysts, and such clinical entities as steatocystoma multiplex. Double comedones are explained by loss of twin hairs.

The loss of drainage incident to failure of a hair to pierce its normal ostium likewise affords an explanation for cystic lesions in some cases of acne and certain dermoids in which the hair, though present, curls up within the cyst. This lack of drainage, promoted by hairs growing through their natural ostia, at least partially explains the development of pilonidal cysts. The latter are very frequently seen associated with severe forms of acne.

By its laminated construction and its continual growth-push from within, the normal hair piercing its normal ostium is a useful and important drain, keeping the exit passage open, pushing and dragging accumulated substances to the surface and thereby preventing a variety of related disorders associated with the pilosebaceous apparatus.

3. Nomland, R.: Treatment of Acne Vulgaris with Comedos by Monoterminal Electrodesiccation, Arch. Dermat. & Syph. **48**:302 (Sept.) 1943.

CALCIFYING EPITHELIOMA

Report of Thirteen Cases

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HONOLULU, T. H.

FIVE EXAMPLES of a peculiar cutaneous or subcutaneous tumor have been encountered during the past year which have been described in the literature as "calcifying" or "calcified" epithelioma. When the first of these tumors was seen, a diagnosis of carcinoma arising in an epidermal cyst was considered; Dr. W. Harold Civin, of the Queen's Hospital, Honolulu, T. H., suggested the correct diagnosis. A review of the surgical material at the Straub Clinic from 1945 through 1950 (during which time approximately 9,000 specimens were examined) revealed eight additional cases which had been reported under a variety of names (Table 1). These 13 cases are being presented because the tumor is unusual and little known, and because it may be misdiagnosed as carcinoma. There are, moreover, certain clinical and pathologic features of considerable interest about which there is some controversy.

HISTORICAL ASPECTS

Malherbe and Chenantais [1] first described this tumor, in 1880, as calcifying epithelioma of sebaceous glands, reporting six cases seen over a 12-year period. In five of these cases the tumor occurred on the head or neck and one on the upper arm, and mention is made of the comparative youth of the patients, one tumor occurring in a child of 15 months. Subsequent reports appeared in the French and German literature, but it was not until 1933 that Ch'in [2] published the first comprehensive report in English. This author described 10 cases encountered over a 15-year period at the Peiping Union Medical College, during which time more than 22,000 surgical specimens were examined. Ch'in collected and analyzed 116 additional cases from the literature.

A single case was reported by Sutton and Sutton [3] in 1935, and 12 were reported by Côté [4] in 1936. Highman and Ogden [5] described 1 probable and 11 definite cases in 1944 from a series of 24,185 surgical specimens received at the National Institute

From the Department of Pathology, Straub Clinic.

1. Malherbe, A., and Chenantais, J.: Note sur l'épithéliome calcifié des glandes sébacées, Bull. et mém. Soc. anat. Paris **15**:169, 1880; Progrés méd. **8**:826-828, 1880.

2. Ch'in, K.: Calcified Epithelioma of Skin, Am. J. Path. **9**:497-524 (July) 1933.

3. Sutton, R. L., and Sutton, R. L., Jr.: Calcifying Epithelioma, Arch. Dermat. & Syph. **31**:48-57 (Jan.) 1935.

4. Côté, F. H.: Benign Calcified Epithelioma of Skin, J. Path. & Bact. **43**:575-586 (Nov.) 1936.

5. Highman, B., and Ogden, G. E.: Calcified Epithelioma, Arch. Path. **37**:169-174 (March) 1944.

of Health over a 16-year period. King [6] reported nine examples of this tumor in 1947, two of them representing transition forms from epidermal cysts, found in 7,500 surgical specimens and suggested the term "mummified epidermal cysts" as being more appropriate than calcifying epithelioma. Allen [7] discussed the tumor briefly in 1948 in a review of the dermatologic material received by the Army Institute of Pathology during World War II. Of 8,000 skin specimens received, 330 were classified under cysts, of which 38 were regarded as being calcifying epitheliomas.

TABLE 1.—*Clinical Features of Thirteen Cases of Calcifying Epithelioma*

Case	Age Yr.	Sex	Race	Duration	Location	Appearance	Diagnosis
1	3	M	Part Hawaiian	3 mo.	Neck	Cyst-like nodule	Calcifying epithelioma
2	25	M	Chinese	4 mo.	Forearm	Firm nodule	Calcifying epithelioma
3	31	M	Caucasian	1½ yr.	Leg	Firm nodule	Calcifying epithelioma
4*	12	F	Japanese	Several mo.	Forearm	Firm nodule	Calficying epithelioma
5†	4	M	Japanese	Unknown	Temple	Hard cyst-like nodule	Calcifying epithelioma
6	15	F	Japanese	1 yr.	Neck	Firm nodule	Degenerated, calcified squamous epithelium
7	9	F	Part Hawaiian	Unknown	Forearm	Firm nodule	Calcified foreign body granuloma
8	15	F	Japanese	Unknown	Forearm	Firm subcutaneous tumor	Epidermal cyst with foci of basal cell carcinoma
9	13	F	Japanese	1 yr.	Scapular area	Hard disc-like subcutaneous plaque	Calcified epidermal cyst with foreign body reaction
10	37	M	Filipino	2 mo.	Temple	Unknown	Carcinoma arising in an epidermal cyst
11	16	F	Chinese	Unknown	Temple	Movable, hard subcutaneous nodule	Calcified epidermal cyst
12	27	F	Japanese	Unknown	Neck	Calcified nodule	Calcified sebaceous cyst?
13	13	F	Chinese	Unknown	Temple	Sebaceous cyst	Epidermal cyst with foreign body reaction

* Reported by courtesy of Dr. Wilfred T. Ohta.
† Reported by courtesy of Dr. Thomas H. Maeda.

CLINICAL FEATURES

The tumors under discussion are firm, sometimes of stony hardness, sharply circumscribed, usually subcutaneous, and freely movable over the deeper tissues but firmly attached to the overlying intact skin. They may occur at any age but predominate in the earlier decades and are relatively common in children. In the 13 cases presented here, the ages ranged from 3 to 37 and 9 were below 17 (Table 1).

6. King, L. S.: Mummified Epidermal Cysts (So-Called "Calcified Epitheliomas"), Am. J. Path. **23**:29-37 (Jan.) 1947.

7. Allen, A. C.: Survey of Pathologic Studies of Cutaneous Diseases During World War II, Arch. Dermat. & Syph. **57**:19-56 (Jan.) 1948.

The tumors occur most frequently on the head, neck, or arms (11 of my 13 cases) but have been reported in many other locations as well. The duration varies widely, from a few months to many years.

TABLE 2.—*Summary of Pathologic Findings in Thirteen Cases of Calcifying Epithelioma*

Case	Size, Cm.	Viable Epithelium	Degenerated Epithelium	Foreign Body Reaction	Calcium	Bone
1	1.2	++	++	++	+	—
2	1.1	+	++	++	+	—
3	0.8	+	++	+	+	—
4	1.0	—	++	++	+	—
5	0.9	+	++	++	+	—
6	1.0	—	++	++	++	—
7	0.8	—	++	++	++	—
8	1.1	+	++	++	++	—
9	1.5	—	++	++	+	—
10	1.0	++	++	++	—	—
11	0.9	+	++	++	++	—
12	0.5	—	++	++	++	+
13	0.5	++	++	++	++	—

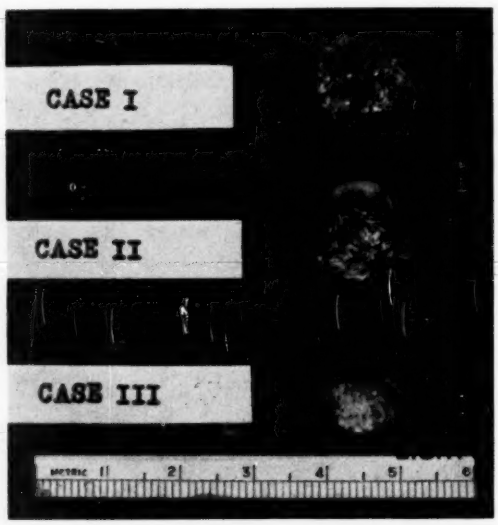

Fig. 1.—Gross appearance of three calcifying epitheliomas.

GROSS APPEARANCE

The tumors are spherical or oval, and their size varies from a diameter of less than 1 cm. up to 3 to 4 cm. or even larger, although the majority are around 1 to 2 cm. (Table 2). Many show gross evidence of calcification, and some are completely ossified. The softer ones have a cheesy compressed sawdust-like appearance upon sectioning, which is quite characteristic (Fig. 1).

MICROSCOPIC APPEARANCE

Microscopically these lesions are made up for the most part of disheveled fragments and irregular columns of degenerated stratified squamous epithelium which are surrounded by connective tissue stroma (Figs. 2 and 3). These fragments of

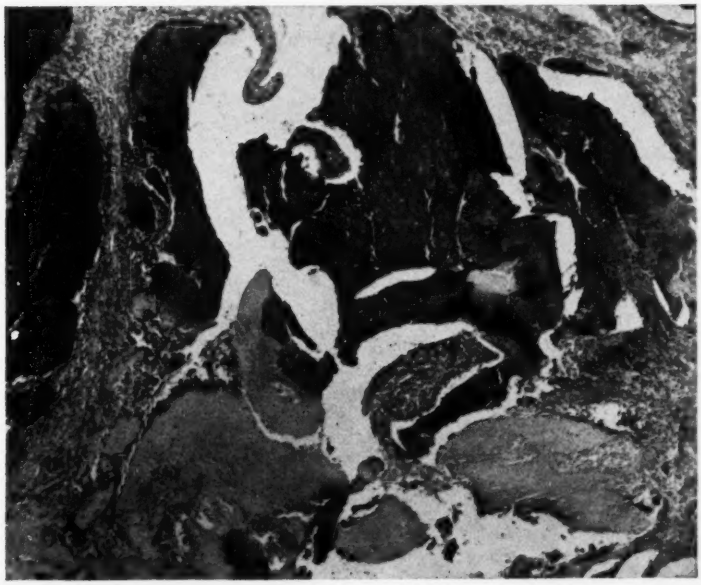

Fig. 2.—Photomicrograph showing fragments of degenerated epithelium (below) and ribbons of viable epithelium above which are separated by a cellular connective tissue stroma. Hematoxylin and eosin; × 45.

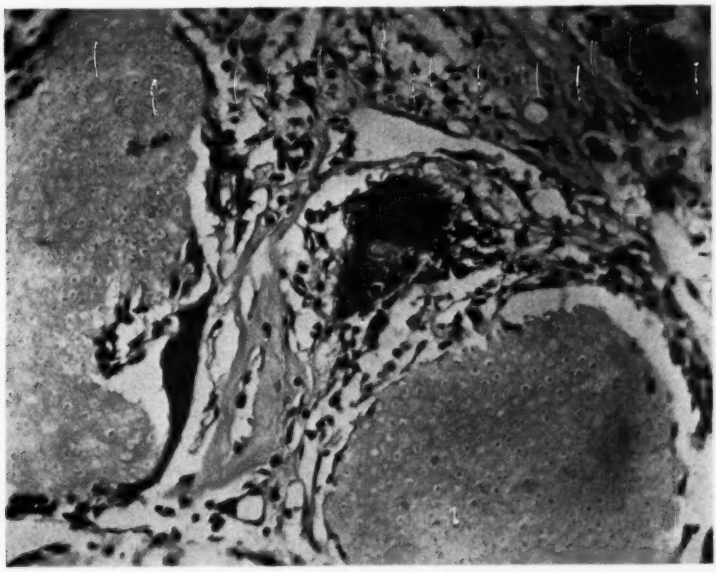

Fig. 3.—Photomicrograph with iris diaphragm partly closed showing distinct cell outlines within degenerated epithelium and foreign body giant cells. Hematoxylin and eosin; ×.265.

degenerated epithelium are acidophilic in their staining properties and at first glance appear as amorphous eosinophilic masses. With the iris diaphragm partly closed,

Fig. 4.—Low-power view of three calcifying epitheliomas. The viable epithelium is shown in black. Hematoxylin and eosin; × 5.

however, the cell outlines and nuclei of individual cells can be seen quite distinctly (Fig. 3). These degenerated epithelial masses are invariably surrounded by foreign

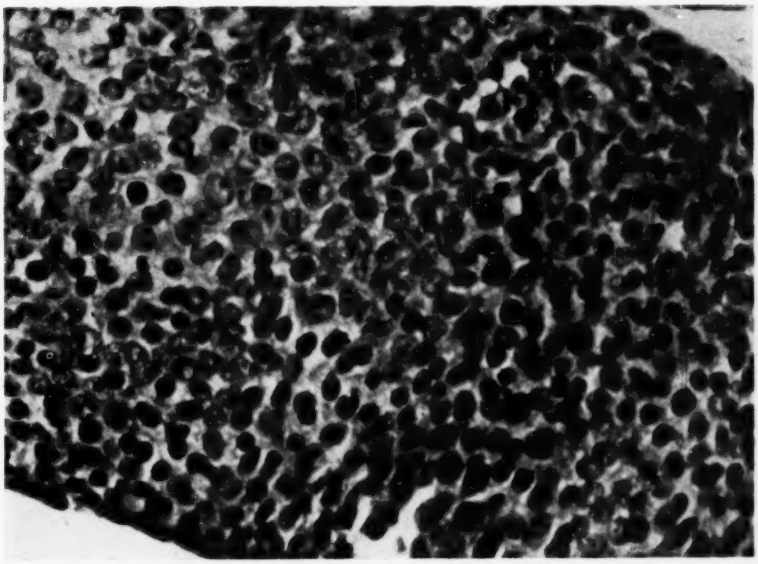

Fig. 5.—Photomicrograph showing character of viable epithelial cells. Many nuclei have a vesicular appearance. Hematoxylin and eosin; × 520.

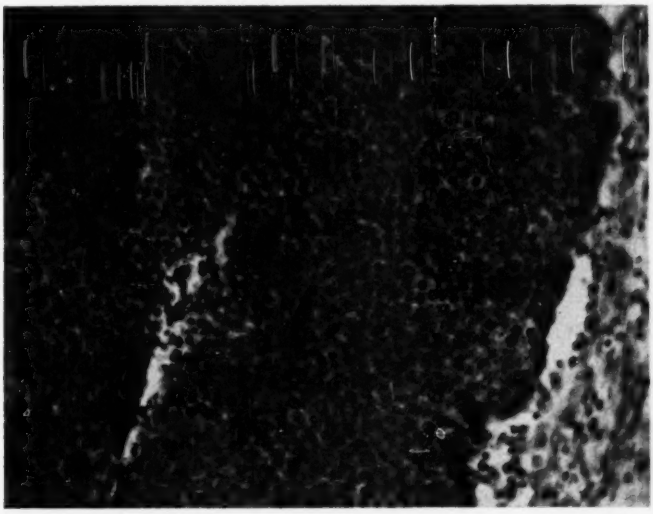

Fig. 6.—Photomicrograph showing the resemblance of the viable epithelial cells to basal cell carcinoma. Hematoxylin and eosin; × 265.

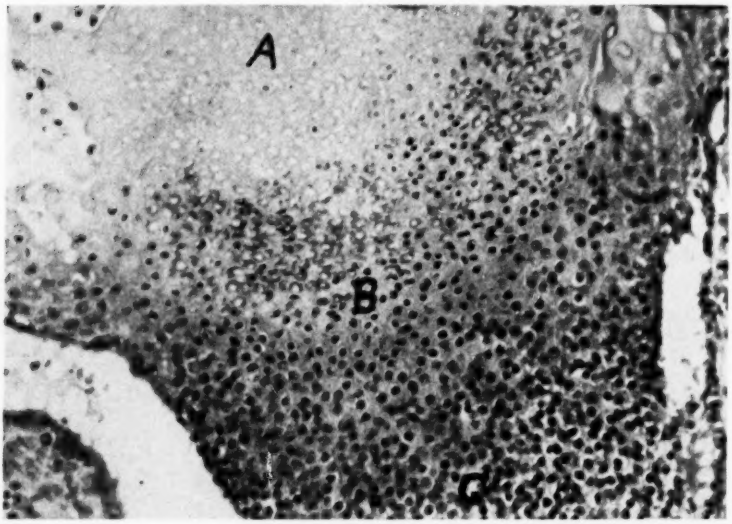

Fig. 7.—Photomicrograph showing gradual transition from degenerated cells (*A*) to cells of prickle character (*B*) to cells of basal type (*C*). Hematoxylin and eosin; × 265.

Fig. 8.—Photomicrograph showing deposition of calcium granules within degenerated epithelial cells (lower left) and partial conversion of these cells into calcific masses (right). Hematoxylin and eosin; × 90.

body giant cells (Fig. 3), and a very intense foreign body reaction is present within the intervening connective tissue stroma. In addition to the giant cells, there are many lymphocytes, plasma cells, and histiocytes, some of which may have a foamy cytoplasm owing to intracellular lipid material. Such degenerated epithelial fragments with the associated foreign body reaction are present in all calcifying epitheliomas, and constitute the most characteristic feature of the tumor.

Of greatest interest, however, is the viable epithelium which was present in 8 of the 13 cases studied (Table 2). The distribution of this epithelium in three tumors is shown in black in Figure 4. It has a tendency to be located toward the periphery but in some tumors is scattered more or less diffusely throughout the lesion. The cells are frequently basaloid in character (Fig. 5) and show a rather striking

Fig. 9.—Photomicrograph showing bone formation. This was found in only one case. Hematoxylin and eosin; × 265.

resemblance in some fields to basal cell carcinoma (Fig. 6). However, gradual transitions from cells of this type to cells of obvious Malpighian character and to degenerated cells are frequently seen (Fig. 7), and it seems apparent that the basaloid cells are not truly of basal nature but are prickle cells which have taken on basal cell characteristics. The viable cells are closely packed together, have rather clear vesicular nuclei with prominent nucleoli, and may show mitotic figures.

Calcium was present in all but one tumor (Table 2), and it may be quite abundant (Fig. 8). It exists predominantly in the form of fine granules deposited within the degenerated epithelial cells, the earliest change, but may appear in the form of solid calcific masses. Occasionally calcific incrustation of stromal connective tissue fibers may be seen. True bone was observed in only one tumor (Fig. 9) but has been reported frequently by others.

COMMENT

There has been much discussion about the pathogenesis and true nature of these tumors. Warvi and Gates [8] interpreted most of the descriptions and photomicrographs of the reported calcified epitheliomas as being compatible with calcification of the contents of epidermal cysts. My own observations are not in accord with this view; the pathologic features of the tumors studied were quite different from ordinary calcified epidermal cysts, and I agree with Ch'in [2] that these lesions form a group of tumors which are clinically and pathologically distinct. It is interesting to note that Malherbe and Chenantais [1] clearly distinguished between calcifying epitheliomas and calcified epidermal cysts in their original article, published in 1880. The occurrence in young persons and the pronounced tendency to involve the head, neck, and arms is in favor of the concept that the tumor constitutes a clinical and pathologic entity.

King [4] suggested the term "mummified epidermal cysts" as being more appropriate than calcified epithelioma. Only one of his nine cases, however, showed viable epithelium made up of ribbons of basal type cells, and this tumor was regarded as a basal cell carcinoma; it was thought by King to belong in a different group from the other eight cases. I believe that the term "mummification" describes the degenerated cell masses very aptly (much more so than "dyskeratotic," applied to these cell masses by Highman and Ogden [5]), but I do not believe that tumors containing ribbons of basal type cells form a separate group. In fact, viable epithelium of this type has been present in the majority of the reported cases and was present in 8 of the 13 cases presented here; it can be regarded as a rather constant feature of the tumor.

So far as the name calcified or calcifying epithelioma is concerned, it is a good one if used in the sense of a tumor of epithelium, but a poor one if epithelioma is used to mean carcinoma—by far the commonest usage—since it is very doubtful that these tumors are actually malignant. They are probably not even locally invasive, although a few recurrences have been reported,[4] and I know of no case which has shown metastases. The name, therefore, is not a good one, but a better term has not yet been suggested.

There is considerable doubt in my mind that these tumors are actual neoplasms. It seems probable that they develop from bits of epithelium detached from the lining of disrupted epidermal cysts, or possibly from the skin itself. It is well known that such bits of detached and buried epithelium have pronounced proliferative tendencies, and it is easy to explain the pathologic picture of the fully developed lesion on this basis. One can postulate the following sequence of changes: proliferation, followed by gradual necrobiosis and mummification due to failure of the blood supply, a foreign body reaction, and finally calcification. The viable epithelium is probably not as viable as it appears to be at first glance, since gradual transitions from living to necrobiotic to degenerated cells are quite evident. It is still difficult to explain the predilection for young persons and the frequent localization on the head, neck, or arms. It is of course conceivable that epithelium in youth has greater proliferative potentialities than epithelium in old age.

8. Warvi, W. N., and Gates, O.: Epithelial Cysts and Cystic Tumors of Skin, Am. J. Path. **19**:765-781 (Sept.) 1943.

From the practical standpoint it is important to recognize that these tumors are not carcinomas. This error is easy to fall into if one is not familiar with the lesion and if large amounts of living epithelium are present (2 of the 13 tumors studied were originally reported as carcinomas arising in epidermal cysts).

SUMMARY

Thirteen examples of a peculiar cutaneous or subcutaneous tumor referred to most frequently as "calcifying" or "calcified" epithelioma are presented. These tumors occur most frequently on the head, neck, or arms and have a predilection for young persons. Pathologically they are made up chiefly of irregular fragments of mummified squamous epithelium which induce a very intense foreign body reaction in the surrounding stroma. Viable epithelium of basaloid type is present in many of them, and the majority contain calcium of greater or less amount. These tumors are not carcinomas, and it is doubtful that they are even true benign neoplasms. They do form a group of tumors, however, which are clinically and pathologically distinct, and which may be misdiagnosed pathologically as carcinoma.

FURTHER AMPLIFICATION OF THE CONCEPT OF DERMATOPHYTID

I. Erythema Annulare Centrifugum as a Dermatophytid

OTIS FIELD JILLSON, M.D.
AND
ROBERT A. HOEKELMAN, M.D.
HANOVER, N. H.

DERMATOPHYTID is the name given the group of skin diseases resulting from allergic reactions to fungous infection of the skin—so-called dermatophytosis. The following minimal criteria must be fulfilled in order to establish the diagnosis of dermatophytid:

1. Focus of dermatophytosis
2. Positive skin test to trichophytin
3. Precipitation of dermatophytid due to blood-borne fungi or fungous products released by
    a. Activation of dermatophytosis
    b. Overtreatment of the dermatophytosis
4. Absence of fungi in the dermatophytid lesions
5. Clearing of dermatophytid after the dermatophytosis has been eradicated

Various investigators have proposed that the following are types of dermatophytids:

1. Disseminated papular lesions [1]
2. Vesicular lesions of the hands [2]
3. Erysipelas-like dermatitis of the lower extremities (may eventuate in chronic lymphedema) [3]
4. Migrating thrombophlebitis and thromboangiitis obliterans [4]

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Dr. Hoekelman is Fellow in Pediatrics, Dartmouth Medical School.

Read before the Section on Dermatology and Syphilology at the One Hundred and First Annual Session of the American Medical Association, June 10, 1952.

1. Jadassohn: Cor.-Blatt. Schweiz. Aerzte **42**:22, 1912.

2. (*a*) Williams, C. M.: Dermatophytid Complicating Dermatophytosis of the Glabrous Skin, Arch. Dermat. & Syph. **13**:661-669, 1926. (*b*) Peck, S. M.: Epidermophytosis of the Feet and Epidermatophytids of the Hands, ibid. **22**:40-76, 1930.

3. (*a*) Traub, E. F., and Tolmach, J. A.: An Erysipelas-Like Eruption Complicating Dermatophytosis, J. A. M. A. **108**:2187-2189, 1937. (*b*) Sulzberger, M. B.; Rostenberg, A., Jr., and Goetze, D.: Recurrent Erysipelas-Like Manifestations of the Legs: Their Relationship to Fungous Infections of the Feet, ibid. **108**:2189-2193, 1937. (*c*) Waisman, M.: Recurrent, Fixed Erysipelas-Like Dermatophytid, Arch. Dermat & Syph. **53**:10-18, 1946.

4. Naide, M.: The Causative Relationship of Dermatophytosis to Thromboangiitis Obliterans, Am. J. M. Sc. **202**:822-831, 1941. Thompson, K. W.: Studies of the Relationship of Dermatomycosis to Ulceration and Gangrene of the Extremities, Yale J. Biol. & Med. **16**:665-753, 1944. Holmans, J. C., Jr.: Use of Trichophytin in Thromboangiitis Obliterans, Arch. Dermat. & Syph. **55**:512-513, 1947.

5. Urticaria (often associated with asthma and vasomotor rhinitis) [5]
6. Miscellaneous group (erythema multiforme, erythema nodosum, exfoliative dermatitis, lesions simulating pityriasis rosea, and erythema annulare centrifugum) [6]

ERYTHEMA ANNULARE CENTRIFUGUM

Clinical Picture.—Erythema annulare centrifugum (erythema gyratum perstans) is a skin disease presenting the following characteristics:

1. The primary lesions are single or multiple edematous erythematous papules.
2. These lesions may be widely distributed, but they have a predilection for the thighs, buttocks, and legs.
3. The papules fade at their centers, while enlarging peripherally to form erythematous annular lesions or, by coalescence, to form polygyrate lesions. The centers of the annular lesions are light yellow and show residual scaling.
4. Without definitive therapy, the lesions persist for years with exacerbations (chiefly during warm weather) and remissions.
5. There are no symptoms except occasional mild pruritus.

Differential Diagnosis.—Erythema annulare centrifugum must be differentiated from pityriasis rosea, seborrheic dermatitis, fungous infection (especially that produced by Trichophyton rubrum), parapsoriasis, erythema multiforme, urticaria, early lesions of lupus erythematosus, granuloma annulare, and leprosy.

Pathology.—The chief pathological characteristic is focal infiltration of lymphocytes around the blood vessels and dermal appendages. In addition, intercellular and intracellular edema with microscopic vesiculation of epidermis occurs (Fig. 1).[7]

Etiology.—Although the consensus is that erythema annulare centrifugum is of unknown causation, the Suttons have stated, "We believe that the disease is a dermatophytid." [6c] They observed that in three cases erythema annulare centrifugum promptly disappeared after effective therapy of vesicular tinea pedis. We propose to offer further evidence that in some cases erythema annulare centrifugum is a dermatophytid.

EVIDENCE THAT IN SOME CASES ERYTHEMA ANNULARE CENTRIFUGUM IS A DERMATOPHYTID

Five patients were observed with erythema annulare centrifugum that fulfilled the minimal criteria for the diagnosis of dermatophytid. Also, two of the patients had vesicular dermatophytid of the hands. One of the patients experienced exa-

5. (*a*) Yearbook of Dermatology and Syphilology, edited by F. Wise and M. B. Sulzberger, Chicago, Year Book Publishers, Inc., 1936, p. 15. (*b*) Wise, F., and Sulzberger, M. B.: Urticaria and Hayfever Due to Trichophyton (Epidermophyton Interdigitale), J. A. M. A. **95**:1504, 1930. (*c*) Waldbott, G. L., and Ascher, M. S.: Chronic Urticaria Recurring Every 6 Weeks, Due to a Fungous Infection, Arch. Dermat. & Syph. **36**:314-317, 1937.

6. (*a*) Peck, S. M., and Schwartz, L.: A Practical Plan for the Treatment of Superficial Fungous Infections, Pub. Health Rep. **58**:337-345, 1943. (*b*) Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Ed. 7, Philadelphia, Lea & Febiger, 1948, p. 1133. (*c*) Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, Ed. 10, St. Louis, C. V. Mosby Company, 1939, p. 150.

7. Hopkins, J. G.: Erythema Annulare Centrifugum (Squamous Form), Arch. Dermat. & Syph. **40**:162-164, 1939.

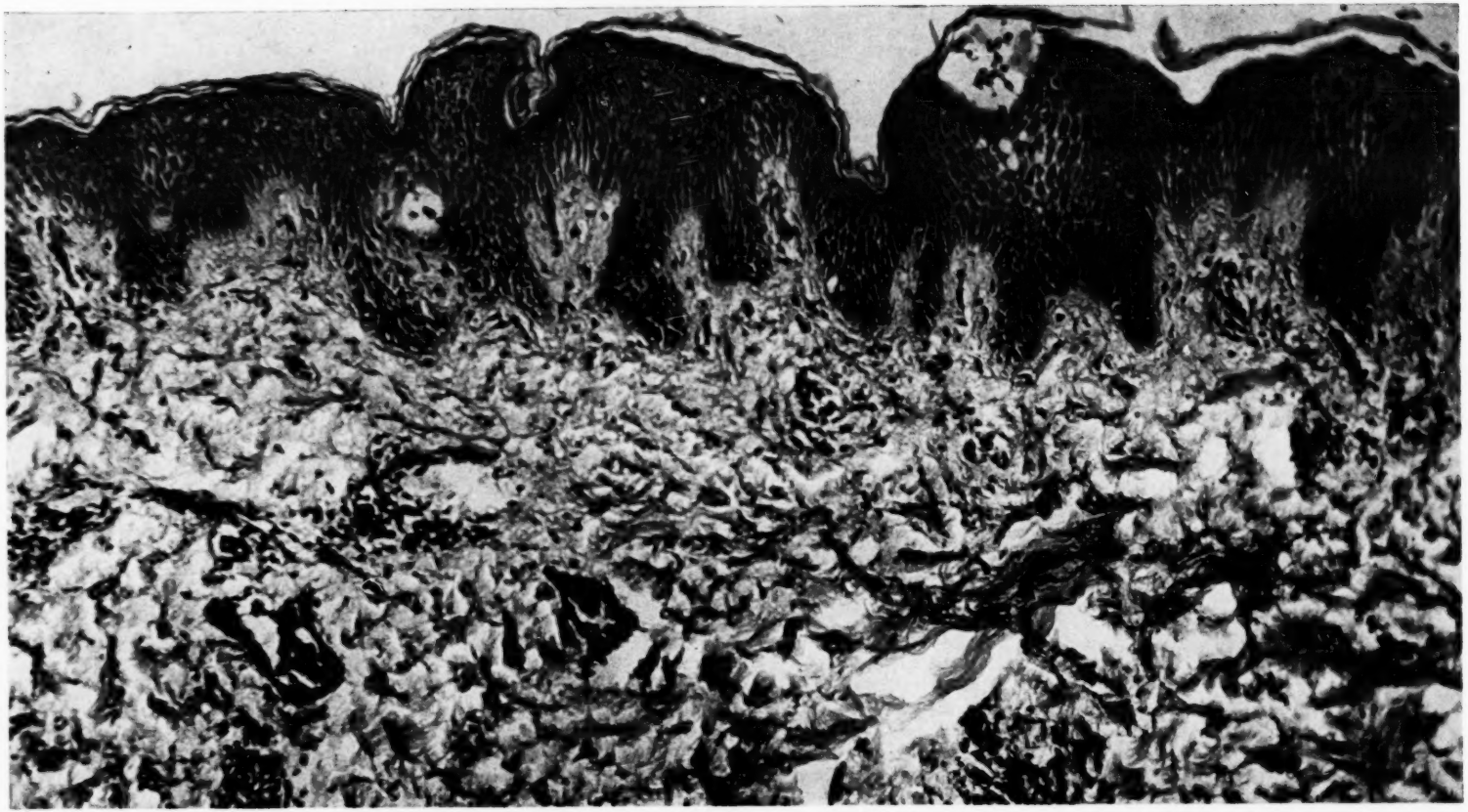

Fig. 1.—Photomicrograph of erythema annulare centrifugum (× 450). Note the focal infiltration of lymphocytes and the microscopic vesicle in the epidermis.

cerbation of his erythema annulare centrifugum lesions after the intradermal injection of 0.1 cc. of trichophytin (Lederle) in a 1 : 30 solution. This exacerbation was characterized by vesiculation and crusting.

Experimental evidence, in addition to clinical, has been obtained to verify further the concept that in some cases erythema annulare centrifugum is a dermatophytid. This was accomplished by (1) the deliberate experimental production of dermatophytosis, (2) observation of the appearance and evolution of erythema annulare centrifugum following this induced ringworm infection, (3) observation of its persistence while maintaining the focus of fungous infection, (4) observation of its prompt disappearance after complete eradication of the experimentally produced dermatophytosis, and (5) repeated production of this entire experiment.

Experimental Procedure.—From Patient R. H., known to have erythema annulare centrifugum, the usual fungus causing typical tinea pedis (Trichophyton mentagrophytes) was

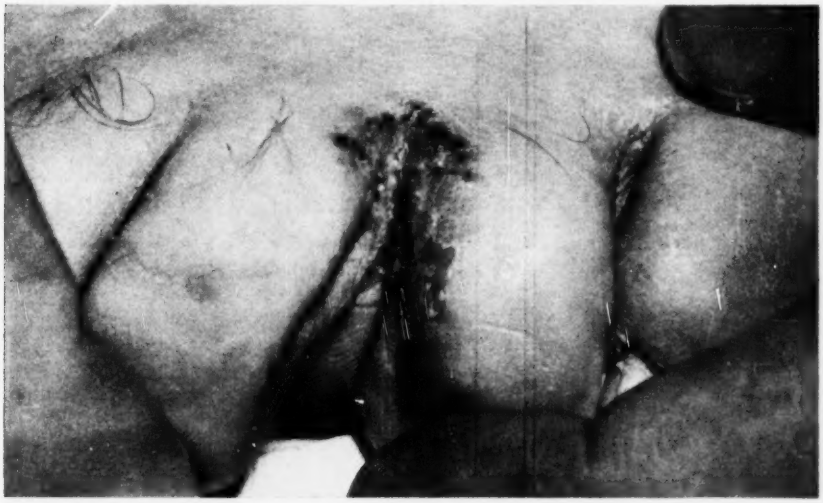

Fig. 2.—Experimentally produced tinea pedis.

cultured. A moist cotton pad was inoculated with this fungus from a 2-week-old culture and placed in the third interspace of the left foot of the patient. Two days later, an active tinea pedis was present, as demonstrated by the clinical picture (Fig. 2), by a positive potassium hydroxide preparation for fungus, and by the subsequent isolation of T. mentagrophytes by culture. On the third day, several edematous papules appeared on the thighs and buttocks. In one week they had progressed to annular and gyrate forms (Figs. 3 and 4). They remained unchanged during the second week. During this time, tinea pedis was active, as shown by potassium hydroxide preparations positive for fungus. (The patient did not wash between the toes of the left foot and wore wool stockings.) Débridement and application of undecylenic acid ointment were then instituted, followed in a week by the disappearance of the experimentally produced dermatophytosis and the lesions of erythema annulare centrifugum. At this time, no clinical or laboratory evidence was found of tinea pedis. This same sequence of events was observed after experimental production of tinea pedis using nonautogenous T. mentagrophytes.

In addition, a second patient known to have erythema annulare centrifugum was inoculated in a similar manner with a fungus isolated from his feet (T. mentagrophytes), and the results were identical with those noted in Patient R. H.

Fig. 3.—Lesions of erythema annulare centrifugum one week after production of experimental tinea pedis.

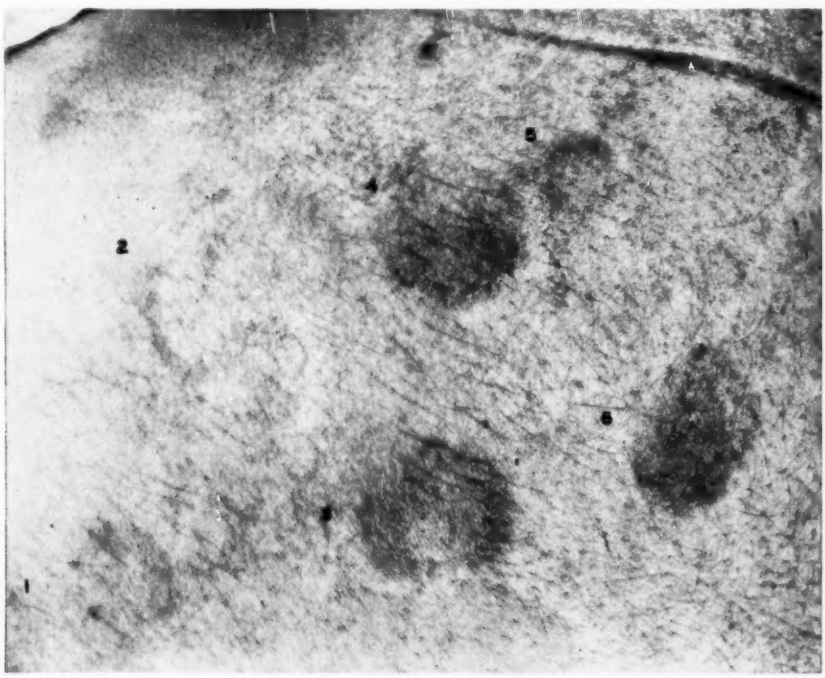

Fig. 4.—Same lesions as in Figure 3 as they appeared one week later.

COMMENT

Even though clinically erythema annulare centrifugum has the appearance of urticarial lesions (thus dermal in origin), histopathologically there are epidermal changes characteristic of eczematization, consisting of intercellular and intracellular edema with microscopic vesiculation. That this is a combined dermal-epidermal disease is further supported by the presence of the delayed 24- to 48-hour tuberculin type of reaction to trichophytin in patients with erythema annulare centrifugum. With dermatophytids that are strictly urticarial in nature, the immediate wheal type of reaction appearing in 15 minutes is observed after trichophytin injection.[5a]

We should like to recall here that at least three types of skin reactions follow the intradermal injection of trichophytin:

1. The immediate wheal type of reaction appearing 15 minutes after the injection of the fungous extract. As stressed by Sulzberger,[5a] this type of reaction is found associated with the urticarial dermatophytids and also the erysipelas-like dermatophytids. Waisman[3c] reproduced the erysipelas-like dermatitis in its entirety by injection of the trichophytin at the site of this disease.

2. The common 24- to 48-hour tuberculin type of reaction to trichophytin. This is noted with the vesicular dermatophytid lesions on the hands.

3. The delayed eczematoid response appearing one week after the initial injection of trichophytin. Our impression is that this type of reaction may be associated with dermatophytid lesions simulating pityriasis rosea.

These facts are well summarized by a statement of Peck:[8]

> It is little known, however, that very often in the more unusual types of trichophytid—namely, those which resemble pityriasis rosea, those which are more eczematoid in type, and those which are somewhat erysipeloid—the trichophytin test simulates the actual trichophytid.

What type of reaction is observed in patients having erythema-annulare-centrifugum-type dermatophytids? As previously stated, the erythematous papule characteristic of the tuberculin type of reaction appears in 24 to 48 hours; but in some patients, instead of fading, it clears centrally, while spreading peripherally to form at one week a small lesion simulating erythema annulare centrifugum. Further interpretation of these types of reactions to trichophytin has been discussed elsewhere.[9]

When Peck experimentally produced vesicular dermatophytid of the hands, two weeks were required for the appearance of these lesions,[2b] whereas the lesions of erythema annulare centrifugum developed within a few days after tinea pedis was induced.

In all five of our patients, the focus of fungous infection was on the feet, and the causative fungus was T. mentagrophytes. In addition, three patients had superficial onychomycosis from which T. mentagrophytes was isolated (Fig. 5). Whether this infection of the nail served as a focus for absorption of fungi and their products from the region of the cuticle, or only as a focus to reinfect the skin, was not determined; however, it was found necessary to eradicate this focus of infection.

8. Peck, S. M.: Symposium on Allergic Dermatoses: Fungous Allergy, J. Allergy **11**:309-318, 1940.

9. Jillson, O. F., and Huppert, M.: The Immediate Wheal and the 24-48 Hour Tuberculin Type Edematous Reactions to Trichophytin, J. Invest. Dermat. **12**:179-185, 1949.

If a patient has this allergic response of erythema annulare centrifugum to the fungi causing dermatophytosis, then a very mild, insignificant tinea pedis (or, rarely, dermatophytosis elsewhere on the body) may promptly activate this dermatophytid. Such pathogenic fungi have been cultured from asymptomatic feet of these patients, as well as others. All suspicious material should be examined for fungi. The Arsac modification of the Hotchkiss-McManus stain will increase the possibility of detecting their presence [10] in the direct preparation. A single negative culture does not rule out the presence of dermatophytosis.[11]

Therapy must be carefully and continuously carried out on the focus of fungous infection to eradicate the focus and to prevent recurrence of erythema annulare

Fig. 5.—Superficial onychomycosis.

centrifugum. If possible, non-rubber-soled, "open" shoes, such as sandals, should be worn. White cotton stockings should be changed frequently to prevent accumulation of moisture. Daily soap and water washings of the feet, with careful drying and removal of soap and all dead skin from between the toes, are probably the most important single preventive procedure. Initially, potassium permanganate soaks (1:5,000) are of value. Prophylactic fungicidal powders containing undecylenic acid should be used daily. Removal of the friable nail with a nail brush and appli-

10. Kligman, A. M., and Mescon, H.: Improved Technique for Diagnosing Ringworm Infections and Moniliasis, J. A. M. A. **146**:1563-1565, 1951.

11. Weidman, F. D., and Glass, F. A.: Repeat Cultures in Dermatophytosis, Arch. Dermat. & Syph. **57**:300-303, 1948.

cation of mild tincture of iodine U. S. P. are effective therapy for the superficial onychomycosis.

As with vesicular lesions of the hands, not all cases of erythema annulare centrifugum are examples of dermatophytid. In one typical example of this disease, no dermatophyte could be isolated, nor was any allergy to these fungi or to the inhalant molds evidenced by skin tests. However, there is some evidence that cross sensitization may exist between the inhalant molds and the skin fungi.[12] Therefore, the inhalant molds should be considered as possible factors in the production and continuation of erythema annulare centrifugum lesions of dermatophytid origin.

CONCLUSION

Some cases of erythema annulare centrifugum are examples of dermatophytid. In this paper are reported five cases of this disease which have fulfilled the minimal criteria for the diagnosis of dermatophytid. In two of these cases, erythema annulare centrifugum was reproduced and abolished by the experimental production and eradication of tinea pedis.

ABSTRACT OF DISCUSSION

DR. JAMES H. MITCHELL, Chicago: My first thought on reading this paper was that, whereas erythema annulare centrifugum is extremely rare, fungous infection of the feet is almost universal in the adult male. My records show a period of 11 years in which I saw no case of erythema annulare centrifugum. No effort was made to determine the number of cases of fungous infections of the hands and feet seen during the same period.

My second thought was that the voluminous French literature on the subject was disregarded in the paper and in the bibliography. For instance, there was a paper by Christine in 1930 in which the subject was discussed at great length.

My third thought was that some excellent work done by Peck in 1930 on dermatophytid of the hands and associated with dermatophytosis of the feet has apparently not been given the attention it deserves.

I was impressed with the manner in which the authors conducted their experiments.

While I was reading the manuscript, a 42-year-old woman appeared with a recurrence on the back of a lesion answering to the description of erythema annulare centrifugum. The patient was first seen in September, 1951, with a lesion which had been present for three months. Two fractional doses of roentgen rays were given, and the lesion cleared by Oct. 24, 1951.

The patient was next seen with a recurrence of a similar lesion in exactly the same area on April 22, 1952. I examined the patient very carefully and found the right sole entirely clear, but the left sole was slightly scaly with the suggestion of infection by T. rubrum. With a few fractional doses of roentgen rays this lesion has also cleared.

Stains were made of the scales from the left sole, using the McManus-Schiff stain. On a careful search of the stained preparations only a few doubtful mycelia were found, and these are shown in the lantern slides of the photomicrographs. A kodachrome® of the lesion on the back of the patient mentioned is also presented.

Trichophytin tests in this case were uniformly negative, and all cultures were negative.

Eight tubes of Sabouraud medium were planted with the scales, but all were negative for fungi.

DR. OTIS FIELD JILLSON, Hanover, N. H.: I want to thank all the discussers very much, in particular Dr. Adolph Rostenberg Jr., who has suggested that local sensitivity to trichophytin, both within and on the periphery of the lesions, be investigated. There was not time in the discussion to refer to all the literature, but, as you will see in the paper, due credit has been given to Peck and others. In personal interviews with Dr. Jacob H. Swartz and Dr. Samuel Peck, I learned that they have observed proved cases of erythema annulare centrifugum as dermatophytids.

12. Jadassohn, W.; Schaaf, F., and Wohler, G.: Analyses of Composite Antigens by the Schultz-Dale Technic: Further Experimental Analyses of Trichophytins, J. Immunol. **32**:203-227, 1937. Cormia, F. E.; Lewis, G. M., and Hopper, M. S.: Experimental Aspects of Penicillin Sensitization, J. Invest. Dermat. **8**:395-402, 1947.

Clinical Notes, New Instruments and Techniques

DERMAL LEISHMANIASIS

Report of a Case with Exceptionally Prolonged Incubation Period

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VANCOUVER, B. C., CANADA

Cutaneous leishmaniasis (Baghdad boil, oriental sore, etc.) is caused by the protozoan organism Leishmania trophica. This organism is indistinguishable morphologically and culturally from Leishmania donovani, the causal organism of visceral leishmaniasis, or kala-azar.

The condition is widespread in Africa and Asia. In Europe, cases are reported from Italy, mainly in the southern half, although some cases have been reported from the northern half. It is endemic in Sicily and very common in Crete. Isolated cases have been reported from the east coast of Spain and from the eastern Pyrenees in France.

Seven cases have been reported in Canada, all the patients having contracted the disease in endemic areas overseas.[1] Similarly, approximately 30 cases have been reported in the United States.[2] The insect vector of this disease is generally conceded to be the sandfly Phlebotomus papatasii. Despite the fact that Packchanian[3] reports that some six species of Phlebotomus exist in the United States, it is unlikely that any of these cases were contracted on the North American continent.

The incubation period of dermal leishmaniasis is variously stated in days, weeks, or months. It is not generally accepted that this period may extend over several years, and to my knowledge only three cases[4] with an incubation period of more than three years have been reported in the literature.

The case herein described is that of a soldier in whom a leishmanial lesion on the face developed about 3½ years after possible exposure to infection. The Pension Commission at first ruled that this was a postdischarge condition not related to army service. This decision has since been reversed, and the case has been accepted as one of dermal leishmaniasis with an unusually long incubation period.

REPORT OF CASE

W. P., a 30-year-old white man, served in the Canadian Army from 1941 to 1945. During this time he was stationed in Algeria, Sicily, Italy, and southern France from July, 1943, to April, 1945. After this he moved out of territory in which leishmaniasis is endemic and served in Holland and England before returning to Canada.

In September, 1948, he noticed a small pimple on the skin of the right cheek just below the eye. It slowly increased in size, was itchy at times, and was covered by a scab. He was seen at the British Columbia Cancer Institute in February, 1949. At this time there was an oval erythematous lesion measuring 1.7 by 1 cm. The upper border was firm and indurated, and there was central superficial ulceration (Fig. 1). Biopsy established the diagnosis of dermal leishmaniasis (Figs. 2 and 3.).

Treatment consisted of administration of 3,900,000 units of penicillin intramuscularly over a period of seven days. Some improvement was noted, but the lesion did not heal. During the next 14 months it remained about the same size and discharged thin serous exudate from time

From the Department of Pathology, Vancouver General Hospital.

1. (*a*) Smith, D. K.: Arch. Dermat. & Syph. **5**:69, 1922. (*b*) Trow, E. J.: Ibid. **35**:455, 1937. (*c*) Forsey, R. R.: Canad. M. A. J. **63**:287, 1950.

2. Forbes, M. A., Jr.: Arch. Dermat. & Syph. **58**:301, 1948.

3. Packchanian, A.: Texas Rep. Biol. & Med. **4**:35, 1946.

4. Napier, L. E., and Halder, K. C.: Indian M. Gaz. **71**:723, 1936. Forsey.[1c] Forbes.[2]

Fig. 1.—Lesion of dermal leishmaniasis, six months after onset.

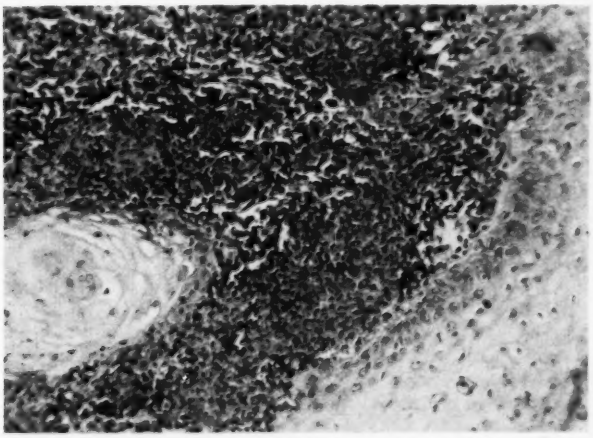


Fig. 2.—Biopsy specimen of lesion, showing chronic inflammatory infiltrate of subepithelial connective tissue; hematoxylin and eosin stain.

to time. In May, 1949, the patient was hit under the right eye by a stick of wood. The preexisting lesion was lacerated and bled profusely. The laceration was healed completely by the end of three weeks, leaving a fine soft scar. There was also complete healing of the leishmanial lesion during this time, and when the patient was examined one year later no evidence of the disease was found.

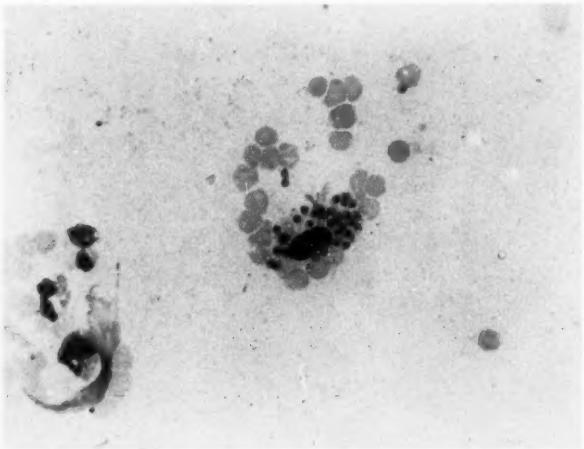


Fig. 3.—Scraping from lesion, showing a large histiocyte containing Leishmania; Wright's stain.

SUMMARY

A case of dermal leishmaniasis is reported, the main points of interest being the long incubation period, three and one-half years, the long duration of the lesion, 20 months, and the spontaneous healing of the lesion following traumatic injury.

SULFOXONE (DIASONE*) SODIUM DERMATITIS

Unusual Distribution in a Patient with Leprosy

FRANK C. COMBES, M.D.
NEW YORK
AND
MICHAEL J. SCOTT, M.D.
SEATTLE

When sulfoxone (diasone*) sodium has been used in the treatment of leprosy, several instances of dermatitis medicamentosa have occurred. Lesions resembling erythema nodosum are known to be produced by this sulfone. However, it is the distribution of the eruption which has been of primary interest to us, rather than the type and nature of the lesion. We have encountered patients with dermatitis medicamentosa from sulfoxone sodium in whom it has been difficult to determine whether the lesions were due to the underlying condition or were actual drug eruptions. This confusion arose in cases in which the distribution of the erythematous nodules due to sulfoxone sodium occurred in areas characteristically involved by leprosy. We are reporting a case of this type of dermatitis in a patient with the lepromatous type of leprosy.

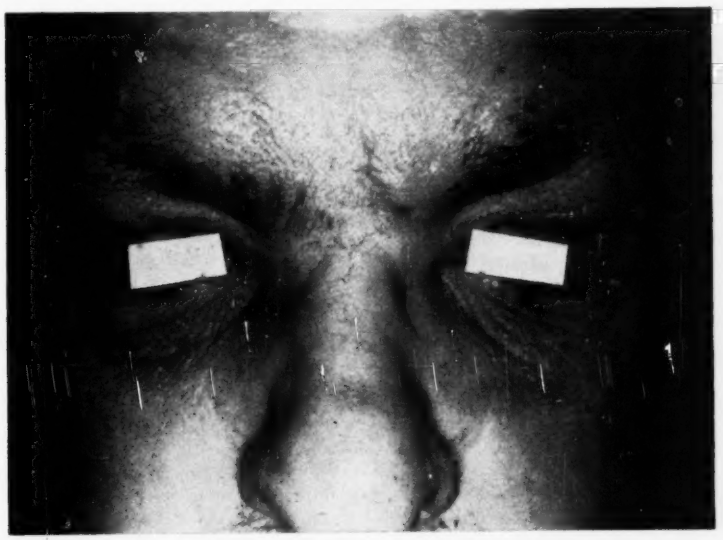
REPORT OF A CASE

R. H., a 52-year-old man, was initially seen in July, 1951. He was born in Czechoslovakia and emigrated to the United States in 1926. In 1949 cutaneous and neurologic evidence of

leprosy appeared, necessitating his admission to the National Leprosarium at Carville, La., for treatment. While there he received various courses of therapy with sulfoxone sodium, amithiozone ("tibione"), and glucosulfone sodium (promine*). No untoward reaction was experienced.

The physical examination at his initial office visit, in 1951, revealed irregular, erythematous, and hyperpigmented patches on his forehead and thighs; partial alopecia was present in the lateral thirds of the eyebrows. Anesthetic areas were detected mainly on the extremities. A few intracellular acid-fast rods could be demonstrated in lymph smears obtained from cutaneous tissues of the ear lobes and arms. A lepromin test was negative.

On Aug. 7, oral medication consisting of sulfoxone sodium, 0.3 gm. three times daily, was begun. In early November erythema-nodosum-like and furunculoid lesions developed in the lateral thirds of the eyebrow regions and on the neck, with a few on the extensor aspects of the forearms and dorsa of the hands. The use of sulfoxone sodium was immediately discontinued. Administration of penicillin, aureomycin, and cortisone had no visible effect upon the eruption. By Nov. 29, no new lesions had developed, and all former lesions were gradually undergoing involution.



Erythema-nodosum-like infiltrations in the superciliary temporal region.

On Jan. 10, 1952, sulfoxone sodium was again prescribed in oral doses of 0.3 gm. daily. In approximately 10 days large nodular lesions had once again appeared in the lateral thirds of the eyebrows and in the temporal and occipital regions. Sulfoxone sodium therapy was discontinued, and again the lesions slowly underwent involution.

A complete blood cell count done on Jan. 31 showed some leucopenia (4,700 leucocytes per cubic millimeter), a large number of immature polymorphonuclear cells (32%), 2.5% myelocytes, and 0.5% eosinophiles (23 per cubic millimeter).

COMMENT

Drug reactions resembling the Jarisch-Herxheimer phenomenon are not uncommon. They have some features of biotropism. Erythema-nodosum-like reactions are common after administration of sulfathiazole, which also causes a flare-up in the erythema-nodosum-like lesions of lymphogranuloma venereum. Similar focal flare-ups are common in patches of discoid lupus erythematosus at the initial administration of gold salts, and recently we observed a dermatitis-like flare-up at the borders of a patch of lupus vulgaris after 10 days' therapy with isonicotinylhydrazine.

Society Transactions

BRONX DERMATOLOGICAL SOCIETY

William Leifer, M.D., *President*

Henry Silver, M.D., *Secretary*

Nov. 15, 1951

Case for Diagnosis: Granuloma? Presented by DR. ALEXANDER A. FISHER.

J. C., a man aged 83, presents an eruption of the scalp which has been present for the past six months. He takes bromo-seltzer® (a preparation containing acetanilid and sodium bromide) occasionally.

The eruption consists of ulcerations, thick-crusted lesions, and a few nodules in a conglomerate mass. Serologic tests for syphilis gave negative reactions. Cultures for fungi were sterile.

Histologic examination of a specimen showed a crust overlying a markedly acanthotic epidermis, which was ulcerated in the center. In the cutis there were numerous dilated vessels and a heavy cellular infiltrate composed of small round cells, histiocytes, and some plasma and polymorphonuclear cells. Beneath the ulceration the infiltrate was composed almost entirely of polymorphonuclear cells. There was no evidence of malignancy or syphilis. The histologic diagnosis was pyoderma.

The patient has received injections of penicillin, bismuth, and aureomycin topically for the past month, without any significant change in the lesions.

DISCUSSION

DR. CHARLES WOLF: The lesion is clinically a prickle-cell carcinoma, consisting of fused smaller lesions at the site. In the left parietal region there is a pyogenic process superimposed upon a prickle-cell carcinoma. I feel that additional biopsies will establish the diagnosis I made.

DR. PAUL GROSS: Providing the biopsy specimen was satisfactory as to site and depth, we have to accept the fact that this is not an epithelial neoplasm. Clinically, the large, slightly infiltrated plaque from which arose several mushroom-like ulcerated tumors strongly suggests mycosis fungoides *d'emblée*. Another biopsy and the therapeutic test with fractional doses of x-rays may establish the diagnosis.

DR. FRANK E. CROSS: I am surprised that the biopsy failed to give us the information which is suggested by the clinical picture. There are two possibilities from the standpoint of malignancy: melanoma and endothelioma. Also to be considered is a drug eruption, but it is not likely.

DR. ALEXANDER A. FISHER: I shall excise the entire nodule and subject it to pathologic study. The report will be submitted at a later date.

Acrokeratosis Verruciformis (Hopf). Presented by DR. ERNEST NATHAN.

S. R., a white girl aged 11 years, complains of warty lesions on the hands and feet of four years' duration. There are no subjective symptoms. No familial history was obtainable.

On examination the patient presents papular and verrucous lesions on the extensor surfaces of the joints of both hands. These vary in size from a small pea to a bean, are flesh-colored, and have a tendency toward coalescence. The flexor surfaces of all the fingers and the palms show a slightly yellowish discoloration, especially marked in the crevices of the joints. In these crevices there are stripe-like transverse elevated yellow bands of firm consistency. Both palms are densely covered with round, slightly elevated papular lesions, varying from pinhead size to 3 mm.

in diameter, also in linear formation. Verrucous lesions similar to those present on the dorsa of the joints are seen on the dorsa and along the borders of the feet.

Urinalysis gave normal findings. Examination of the blood showed 14.1 gm. of hemoglobin per 100 cc. and 6,500 white cells per cubic millimeter, with 48% polymorphonuclear cells, 1% eosinophiles, 47% lymphocytes, and 4% monocytes.

Histologic examination showed hyperkeratosis of the nevoid type, compatible with Hopf's acrokeratosis verruciformis.

DISCUSSION

DR. DAVID BLOOM: The complete biopsy report has not yet been received. Dr. Hyman's report states that the histologic findings are compatible with a nevoid type of keratosis.

DR. HENRY SILVER: Clinically, this case is a good example of acrokeratosis verruciformis. The lesions are fairly characteristic and limited to the hands and feet. The histologic picture, especially the basket-weave epidermis, is even more pronounced in epidermodysplasia verruciformis. But even there we ask: Is it an essential feature of epidermodysplasia? As a diagnostic criterion, I do not think it is reliable. Acrokeratosis verruciformis should be differentiated from epidermodysplasia verruciformis, because in the latter we find lesions on the face which frequently show epitheliomatous changes.

DR. ERNEST W. NATHAN: The lesions in the case presented fit well the description of acrokeratosis verruciformis as given by Hopf. The patient shows verrucous, or rather verruciform, lesions on the dorsa of the hands and feet with a distinct involvement of the palms and flexor surfaces of the fingers. The face, neck ,and trunk are not involved, distinguishing the condition in the presented case from epidermodysplasia verruciformis. The histologic picture conforms with the diagnosis of acrokeratosis showing nevoid keratosis, but not a basket-weave-like arrangement of the stratum corneum, as seen in epidermodysplasia verruciformis.

Follicular Hyperkeratosis in a Patient with Atopic History and Normal Blood Vitamin A. Presented by DR. IRWIN I. LUBOWE.

A W., an obese boy aged 8 years, has an eruption on the back, buttocks, and arms of two months' duration. He has had ragweed hay fever for two years and has been treated with antihistaminics. The eruption is slightly pruritic.

There are several sharply marginated, scaly patches on the lower back and buttocks. These patches have a periphery of vesicles. On the upper back there are sharply circumscribed, depigmented patches, showing follicular accentuation.

Determination of vitamin A levels in the blood showed 86 units per 100 cc. of fasting total carotenoids, 100 units per 100 cc. of four-hour total carotenoids, 10 blue units of fasting vitamin A and 60 blue units of vitamin A after four hours. The mycological examination gave negative results. The tuberculin test was negative. The reaction to the Vollmer patch test was positive and was subsiding after 48 hours. Urinalysis showed no abnormalities.

Examination of the blood showed 12.5 gm. of hemoglobin per 100 cc. (86%), 4,600,000 erythrocytes and 7,000 leucocytes, with 63% polymorphonuclear neutrophiles, 2% polymorphonuclear eosinophiles, 30% lymphocytes, and 5% monocytes.

DISCUSSION

DR. ELLEN REINER: I have observed sharply circumscribed patches with accentuation of the follicles in many children. Tuberculin tests, as well as scrapings for fungi, have always proved negative.

DR. VICTOR H. WITTEN: Have sweat studies been made on this patient?

DR. RUDOLF L. BAER: An important question in this case is whether we are dealing with atopic dermatitis. I assume that Dr. Lubowe wants to stress this point, since he mentions the atopic background of this patient. Lesions which suggest tinea to the nondermatologist are not too uncommon in atopic dermatitis. However, direct examination of scrapings and cultures readily rule out fungous infection. As far as the follicular keratosis is concerned, some patients with atopic dermatitis present a fine papular eruption on the trunk, which consists either of protruding sweat-gland openings or of follicle openings or of both. In this boy, however,

keratotic papules on the back are mostly confined to the circumscribed tinea-like patches; on the abdomen they are more generally distributed. There is no involvement of the characteristic sites of atopic dermatitis, and itching appears to be negligible.

DR. LAURENCE F. PALITZ: I do not think there is any connection between this condition and atopic dermatitis. In the patients under my observation I have not seen concurrent atopic eczema. In many of these patients the lesions disappeared after several months regardless of the intake of vitamin A.

DR. WILBERT SACHS: I recently saw two similar cases at the New York Hospital, both of children, who showed follicular neurodermatitis.

DR. IRWIN I. LUBOWE: The tuberculin and Vollmer patch tests gave negative results, ruling out therefore the suspected diagnosis of lichen scrofulosorum. Mycologic studies also gave negative results. Sweating studies are now being performed by Dr. Herrmann. No biopsy was done, because it was thought that the usual histologic picture would be found. However, in view of Dr. Sachs's suggestion, we intend to do a biopsy on this patient to see whether there is a connection between follicular hyperkeratosis and neurodermatitis.

Familial Edema of the Legs. (Milroy's Disease). Presented by DR. ABRAHAM J. ORFUSS JR.

I. W., a youth aged 20, presents an enlargement of the entire left lower extremity of lifelong duration. There is no pitting. There is no family history of a similar affliction.

The left heel and lateral margins of the foot present large, hyperkeratotic plaques with deep furrows.

DISCUSSION

DR. FRANK E. CROSS: In spite of the tremendous deformity, the patient does not seem to be incapacitated in any way. I therefore feel that we should let well enough alone.

DR. CHARLES WOLF: Certain features which would confirm this diagnosis are conspicuously absent: 1. The patient was not born with the disease; it was first noticed at the age of 10 years. 2. There is involvement of the foot, which is not seen in Milroy's disease. 3. Most important, one can generally trace in the genealogical tree other members of the family with the disease. I believe the condition is a nevus, an elephantiasis of nevoid origin.

DR. HENRY SILVER: This case is a fair example of Milroy's disease. Although the patient is the only member in the family with this disease, we must still adhere to the concept that it is familial. In some European countries, especially in Ireland, it is more prevalent; many families are afflicted. It is there known as the "big foot," and little attention is paid to it.

DR. PAUL GROSS: Only this day I saw a patient with typical Milroy's disease whose history did not suggest heredity.

I agree with Dr. Wolf that this case may be one of a nevoid condition; whatever it is, there is definite involvement of the lymph vessels, as can be seen by the verrucous formation on the foot. This occurs in elephantiasis, infectious lymphedema, lupus vulgaris, Kaposi's disease, and Milroy's disease. It is interesting that this patient has had no attacks of erysipelas or lymphangitis, to which patients with typical Milroy's disease are highly susceptible.

DR. ABRAHAM J. ORFUSS JR.: This patient is most concerned about the verrucous lesions of the heel, which he wants treated. He has adjusted himself very well to his giant left lower extremity and does not desire that anything be done about it.

Case for Diagnosis: Granuloma Inguinale (?), Involving the Perineum. Presented by DR. IRWIN I. LUBOWE.

E. O., a Negro woman aged 34, gives a history of treatment for syphilis in 1939 and again from 1944 to 1949. Treatment at that time consisted of 30 injections of arsenicals and 35 of a bismuth preparation. She states that she had a lesion and a small mass in the vulva in 1939. The lesions disappeared in 1944 and recurred in January, 1951.

A large ulcerative, edematous, granulomatous, fungating, bleeding mass involves the labia majora and minora and extends into the vagina.

Smears for Donovan bodies were positive on Oct. 5, 1951. Serologic tests for syphilis gave negative reactions.

The patient has received a total of 48 gm. of dihydrostreptomycin and 8 gm. of chloramphenicol, commencing Oct. 5. To date, she has not shown appreciable improvement.

DISCUSSION

DR. JULIUS H. POLLOCK: Almost every year at least one case of this type is presented before the Society. While such cases are not met with commonly in private practice, in hospital and clinic practice they are encountered often enough to constitute a serious problem.

Dr. Sobel and I have had considerable experience with this disease, and we have yet to see a patient who failed to respond to streptomycin therapy, in contrast to therapy with the older drugs. It is true that in some cases the disease will respond to smaller courses and in some, especially the older ones, as much as 45 to 60 gm., in 3-gm. daily doses, is given, amounts which may be startling. We have never seen any evidence of nerve involvement. Our lack of complication with the antimonials in this group of patients has been duplicated with the use of streptomycin.

Therefore, I think that the patient should receive a more intensive trial with streptomycin along the lines indicated. If at the end of two or three weeks of intensive therapy there is no decided response, a biopsy should be done. Unfortunately, a single biopsy, or even two, may not reveal malignancy; so Dr. Sobel and I have gone on the premise that if such a condition as is presented here does not respond to adequate streptomycin therapy, even though the biopsy revealed nothing significant, the condition should be treated surgically as a neoplasm.

DR. RUDOLF L. BAER: I have no personal experience with the treatment of granuloma inguinale with streptomycin and dihydrostreptomycin. However, I am interested in the discussion regarding dosage. It is my experience that in general there is a disregard of the simplest principles of correlating the dosage of drugs to the weight of the patient. The only notable exceptions are the pediatricians, who are in the habit of adjusting the dose to the patient's weight.

It seems to me that one should take the weight factor much more into account when prescribing for patients. For example, the patient with granuloma inguinale under discussion appears to be much heavier than average, and therefore the dose of the antibiotic given her should logically be revised upward as compared with the average.

DR. FRANK E. CROSS: I have in mind a patient with an even more extensive granuloma than that in this woman. This was in a man with severe secondary anemia, who received streptomycin and stibophen (fuadin®) at the same time. Stibophen was given three times a week and streptomycin twice a day, for a total of about 50 gm. in a period of six to eight weeks. He made a remarkable recovery in about two months.

DR. PAUL GROSS: I do not agree with the presenter that this is a refractory case. Treatment was started on Oct. 5, and if the past medication should fail to be fully effective a different type of therapy should be instituted.

DR. CARL T. NELSON (by invitation): I agree with Dr. Gross; 48 gm. of dihydrostreptomycin is really a small total dose for this type of lesion. I also wonder why streptomycin has not been given. Dihydrostreptomycin has proved to be rather damaging to hearing and no more effective than streptomycin. I heard recently that some drug companies are thinking of stopping its manufacture.

DR. JULIUS H. POLLOCK: The reason we changed from streptomycin to dihydrostreptomycin was because administration of the streptomycin was very painful, and painfulness is an important factor in keeping up the patient's attendance. We have not found dihydrostreptomycin ineffectual in treatment of granuloma inguinale.

DR. IRWIN I. LUBOWE: In answer to Dr. Pollock, this patient received 4 gm. of dihydrostreptomycin daily for 10 days. She therefore received a total of 40 gm. as of Oct. 15, and then she received 2 gm. three times a week. Recently Pariser, Goldberg, and Mitchell reported 76 cases of granuloma inguinale treated with streptomycin (ARCH. DERMAT. & SYPH. **62**:261-264, 1950). In all but three of these cases the condition cleared up on a dose of 20 gm. In two of these the disease was refractory, and in the third it was treated surgically. There is a possibility that the disease in the present case may respond to stibophen. Dr. Baer brought up a good point as to weight and dosage. The New York City Department of Health has a routine schedule which we follow regardless of weight.

In answer to Dr. Nelson, dihydrostreptomycin is less painful, less toxic, and just as effective therapeutically. There has been improvement of about 40% since the patient was first seen, and she will probably continue to be treated with dihydrostreptomycin in conjunction with chloramphenicol.* However, we shall have to be careful because of the possible permanent toxic involvement of the auditory nerve.

Erythema Multiforme Bullosum of the Scalp. Presented by Dr. William M. Siskind.
Macrodactylia with Macronychia and Fibromata. Presented by Dr. Ernest W. Nathan.
Case for Diagnosis: Erythema Multiforme Bullosum? Pemphigus Vulgaris? Presented by Dr. Irwin I. Lubowe.
Dermatitis Herpetiformis. Presented by Dr. Hans H. Birkstein.
Erythema Induratum (Bazin). Presented by Dr. Abraham J. Orfuss Jr.
Argyria. Presented by Dr. Abraham J. Orfuss Jr.

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

Anthony C. Cipollaro, M.D., *Chairman*
J. Lowry Miller, M.D., *Secretary*
Feb. 5, 1952

Dermatitis Herpetiformis in an Infant. Presented by Dr. Andrew H. Montgomery.

E. R., a boy aged 18 months, is presented from the New York Polyclinic Medical School and Hospital with a generalized eruption of two months' duration. The eruption first appeared in the groin region and lower part of the abdomen and spread to the face, neck, ears, and extremities. There were no lesions on the back for the first two weeks. The scalp and mucous surfaces were clear. There were no constitutional symptoms, but mild pruritus was present. The patient was first treated for bullous impetigo, with recurrence of the lesions. There is no history of use of drugs or previous vaccination.

The lesions consist of clear, tense bullae, erythematous macules, vesicles, and pustules.

Biopsy showed the superficial vessels to be dilated, with surrounding edema. There was a perivascular infiltrate composed of small wandering connective tissue cells, some polymorphonuclear cells, and eosinophiles. Within the papillary bodies were edema and vesicle and bulla formation. In these areas were numerous polymorphonuclear cells and eosinophiles. The epidermis showed no significant changes. The diagnosis was dermatitis herpetiformis.

A blood cell count showed 4,520,000 red cells and 15,200 white cells, with 28 polymorphonuclear leucocytes, 62 lymphocytes, 8 eosinophiles, and 2 monocytes. A smear showed moderate hypochromia, slight anisocytosis, and poikilocytosis, with one plasma cell. Serologic reactions for syphilis were negative. Bacterial culture yielded staphylococci. Examination for virus inclusion bodies gave negative results. A culture for fungi was sterile.

Local treatment consisted of use of ammoniated mercury, U. S. P., sulfur, and silver nitrate. Oxytetracycline (terramycin) was given orally for the first week. Penicillin (3,000,000 units) was given, with good results, but the lesions recurred when the drug was discontinued.

DISCUSSION

Dr. Charles Wolf: The lesions as seen in this case consisted of vesicles, discrete and conglomerate, many of them pustular and others serous. The impression is that of a recurrent, severe type of bullous impetigo. The temporary response to administration of penicillin would indicate such a diagnosis, and the finding of staphylococci in the serum seems to support it.

Dr. Perry Sachs: I should expect secondary impetiginization in that area in a child of that age. However, the vesiculation is subepidermic, which is not the picture of bullous impetigo; and the microscopic findings are typical of dermatitis herpetiformis.

Dr. Arthur B. Hyman: Elastic tissue changes in epidermolysis bullosa are secondary and relatively unimportant. I believe careful study will finally prove it to be pyoderma.

Dr. Mabel G. Silverberg: It looks more like infectious eczematoid dermatitis than impetigo or dermatitis herpetiformis.

DR. ANTHONY C. CIPOLLARO: We considered all the diagnoses which have been mentioned this evening, and by exclusion and because of the histologic findings we made the diagnosis of dermatitis herpetiformis. At first we all agreed that it was pyoderma, probably impetigo.

DR. ANDREW H. MONTGOMERY: As Dr. Cipollaro said, many observers at first thought it was impetigo contagiosa bullosa. That is still my diagnosis. The eruption has improved greatly with penicillin. I was surprised when I heard the histologic diagnosis, and I have my fingers crossed yet on that.

Herpes Zoster in a Six-Month-Old Infant. Presented by DR. MAURICE J. COSTELLO.

L. H., an infant 6 months of age, presents a unilateral, painful cutaneous eruption of one week's duration. Examination reveals numerous grouped vesicles along the sensory branches of the eighth cervical and fourth thoracic spinal nerves on the right side. The arm, pectoralis major area and scapular region on the right side are involved. The contents of some vesicles, such as those over the pectoralis major and the extensor surface of the right arm, are hemorrhagic.

DISCUSSION

DR. CHARLES WOLF: I question whether the eruption is herpes zoster. I have never seen so young an infant with this disease. If the lesions heal within the next three or four weeks, I should be reasonably certain it was herpes zoster. However, I feel that further observation may show that it is an early and anomalous form of epidermolysis bullosa.

DR. HERMAN GOODMAN: Did anybody else in the family have herpes zoster? Was anybody who is close to the child vaccinated? Have any relatives or neighbors had varicella?

DR. L. V. LUTTENBERGER (by invitaton): No, we questioned carefully, and there is no history of the disease in anybody surrounding the patient. We present the case because it is rare.

Erythema Induratum Involving Thighs and Forearms. Presented by DR. ANTHONY C. CIPOLLARO.

E. P., a Cuban-American woman aged 38, is presented from the New York Polyclinic Medical School and Hospital with subcutaneous nodules, which have been present for four months. The patient had rheumatic fever in childhood, with cardiac involvement, and was treated for cardiac decompensation at Bellevue Hospital in 1950. For the past six months she has had night sweats, bouts of fever, and loss of about 30 lb. (13.6 kg.). Four months ago she discovered a painful nodule on the inner aspect of the left thigh, and when first seen, on Jan. 5, 1952, she presented similar tender subcutaneous nodules on both thighs, legs, and forearms and the upper part of the back. None of these lesions was ulcerated, and they ranged in size from that of a pea to that of a walnut. The overlying skin was normal in color.

The hemoglobin was 14.4 gm. per 100 cc., and the blood cell count showed 4,320,000 red cells and 10,500 white cells, with 46 polymorphonuclear leucocytes, 48 lymphocytes, 3 monocytes, and 3 eosinophiles. The Kahn reaction of the blood was negative. The reaction to tuberculin in a dilution of 1:1,000,000 was strongly positive. A roentgenogram of the chest revealed increased hilar densities and bronchovascular markings, with a fine reticular pattern throughout both lungs. There was no definite evidence of infiltration. The apices and infraclavicular regions were free from tuberculous infiltration.

Biopsy of a nodule from the left thigh showed in the cutis edema in some areas and evidence of fibrosis in others. Some areas showed definite necrosis. There was a diffuse cellular infiltration, composed of small, round, wandering connective tissue cells and some giant cells. There were some plasma cells. In many areas were discrete masses of epithelioid cells (tubercles). Some of these masses contained giant cells. Some of the vessels showed swelling of the intima and wall. The epidermis showed no significant changes. The diagnosis was erythema induratum.

DISCUSSION

DR. PAUL GROSS: We are used to seeing erythema induratum exclusively on the legs, but, in view of the histopathologic findings and past history, I don't think the diagnosis is to be doubted in this case. Much would depend on laboratory tests during the course of the disease

and the response to tuberculin therapy. I believe this condition must be differentiated from Weber-Christian disease (nodular nonsuppurative panniculitis), and possibly another biopsy must be performed to prove the diagnosis.

DR. PERRY SACHS: The microscopic findings were rather conclusive. There were definite tubercles deep in the cutis and fat, as well as a great amount of reaction. An unusual feature was the pronounced necrosis seen in the sections, but not evident clinically.

DR. ANTHONY C. CIPOLLARO: Two deep-excision biopsies were performed, and a good chunk of tissue was taken out each time. The first was inconclusive, and the second showed the picture Dr. Sachs pointed out. One of the lesions removed did show clinically some early superficial necrosis, and that probably accounted for the microscopic picture. Most of the lesions this woman had were just subcutaneous nodules, and it was difficult to make a clinical differential diagnosis. To do so, one would have to consider all the diseases that produce nodular lesions. We arrived at the diagnosis presented mainly on the basis of the histologic findings and of the fact that the tuberculin reaction was very strongly positive at a dilution of 1:1,000,000. Roentgenograms of the chest were essentially normal, with no definite indication of any tuberculous infiltration. We consider this case to be one of tuberculosis indurativa (erythema induratum; Bazin's disease) of an unusual clinical variety, with an unusual distribution of the nodules.

Parapsoriasis in a Young Child. Presented by DR. LEO SCHWEICH.

V. D., a girl aged 3 years, is presented from the Lenox Hill Hospital, where she was seen in consultation in February, 1951, while a patient in the pediatric service. A diagnosis of parapsoriasis varioliformis (pityriasis lichenoides et varioliformis acuta) was made. The subsequent course resulted in a final diagnosis of chickenpox superimposed upon parapsoriasis guttata. (An intern who attended this child became ill with chickenpox within the usual incubation period.)

At present the eruption is generalized and consists of erythematous, tannish, lichenoid, and slightly infiltrated oval and round papules, varying in size from that of a pinpoint to that of a small pea. A few lesions are covered with a small amount of fine scale. There are no lesions on the palms and few below the knees. There are no subjective symptoms, and never has there been pruritus.

The hemoglobin was 11.4 gm. per 100 cc. (76%), and the red blood cell count is 3,600,000.

Parapsoriasis in a Young Child. Presented by DR. LEO SCHWEICH.

E. M., a boy aged 4 years, is presented from the Lenox Hill Hospital with a generalized eruption of five months' duration. The onset was in September, 1951, at which time the child presented a generalized macular, salmon-colored eruption, which was not pruritic and which was unattended by other local or general symptoms. At present the eruption is generalized except for the head. Numerous nonpruritic lichenoid, slightly infiltrated, oval and round, tan-pink maculopapules of various sizes cover the entire trunk and are scattered over the extremities. A fine, thick adherent scale is present.

Treatment has consisted of 25,000 units daily of calciferol (vitamin D_2), weekly ultraviolet irradiation, and use of vitamin B complex.

A roentgenogram of the chest was normal, and the Kline reaction of the blood was negative.

DISCUSSION ON PRECEDING TWO CASES

DR. ANTHONY C. CIPOLLARO: Those of you who have seen this disease for the first time might think parapsoriasis occurs only in infants, and commonly.

DR. ARTHUR B. HYMAN: The term parapsoriasis has been applied to many different diseases, and the features they have in common are mostly negative—they do not have a diagnostic histologic picture, they do not respond to treatment, and they do not itch. Thus, it is important to add some qualifying term to the word parapsoriasis. If the condition in these cases is parapsoriasis, what type does it represent? There is nothing to indicate lichenoid parapsoriasis, for there are no nodular, retiform, or poikilodermatous lesions. Unless a case of parapsoriasis is presented with some qualifying term to indicate its type, we cannot usefully discuss it.

DR. LEO SCHWEICH: Both cases clinically are most representative of the guttate type of parapsoriasis—a diagnosis confirmed by the histologic findings. These cases merit special interest because of the unusually early age of the patients. In my experience, cases are rarely seen in patients below the age of 5 years. In one of these children the onset of the disease was at the age of 2 years, and in the other, at 2½ years.

Multiple Osteomas of the Skin of the Face. Presented by DR. T. J. RIORDAN.

C. F., a woman aged 43, presents an eruption on the face of 15 years' duration, for which she was seen at St. Clare's Hospital. Scattered about the face are discrete papules from pinpoint to pinhead in size. There is no history of acne.

Roentgenograms of the skull and facial bones fail to disclose any osseous or intracranial pathology. Multiple small intracutaneous and subcutaneous calcified nodules are noted in the soft tissues of both cheeks. Most of these lesions are discrete, but several appear confluent. X-ray studies of the hands fail to disclose any lesions of the bones.

Biopsy showed bone formation within the cutis.

DISCUSSION

DR. WALTER G. GASNER (by invitation), Mount Vernon, N. Y.: The patient is presented because of the rarity of primary osteomas of the skin with no history of acne or trauma.

Case for Diagnosis: Pemphigus? Erythema Multiforme? Presented by DR. T. J. RIORDAN and DR. ORLANDO CANIZARES.

T. S., a man aged 56, was seen in May, 1951, with an extensive bullous eruption. He was hospitalized, and his condition improved with corticotropin and cortisone treatment. He had a relapse and was hospitalized at Veterans Administration Hospital, Newington, Conn., from Aug. 23 to Oct. 16, 1951. He was admitted to the Veterans Administration Hospital, Bronx, N. Y., on Oct. 16, 1951, at which time he showed denuded and crusted lesions with peripheral bullae on the trunk, and erythema and crusting of the forehead. There was slight pruritus.

At the Bronx Veterans Administration Hospital results of all blood counts, urinalyses, and blood chemistry examinations were normal. Sputum cultures showed pneumococci, but no acid-fast bacilli. Roentgenograms of the chest revealed honeycomb infiltrations in the base of the left lung, suggestive of bronchiectasis. Biopsy of a cutaneous lesion was reported as showing pemphigus vulgaris.

During his first hospitalization the patient received corticotropin, followed by cortisone. At the Newington Veterans Administraton Hospital he received 4 gm. of sulfapyridine daily from Sept. 17 to 28, with no improvement, and 2 gm. of oxytetracycline daily from Oct. 9 to Oct. 16, with no change in his condition.

At the Veterans Administration Hospital, Bronx, the patient was treated with permanganate baths, oral administration of testosterone and chloramphenicol (chloromycetin®), and local applications of hydrogenated cottonseed oil (crisco®), with steady improvement. The teeth were pyorrheal and were removed in December, 1951. Staff members of the chest service recommended only postural drainage for his bronchiectasis. At present there are erythema and crusting of the forehead and a few scattered, small, crusted lesions on the chest and shoulders.

DISCUSSION

DR. ORLANDO CANIZARES: We all know how difficult it is to make a differential diagnosis of the two diseases. I want to stress that the patient has bronchiectasis. I think a focus of infection must be looked for in a bullous eruption of this type. My impression is that he has erythema multiforme bullosum, probably due to bronchiectasis.

Incontinentia Pigmenti. Presented by DR. S. IRGANG.

Lipid Proteinosis. Presented by DR. MAURICE J. COSTELLO.

Atopic Dermatitis with Corneal Opacities, Treated with Cortisone. Presented by DR. MAURICE J. COSTELLO.

Fixed Drug Eruption (Acetylsalicylic Acid). Presented by DR. ANDREW H. MONTGOMERY.

Lichen Sclerosus et Atrophicus of the Perineum and Wrists; Alopecia Areata and Ophiasis. Presented by DR. PERRY SACHS.

Trichophyton Rubrum (Purpureum) Infection Simulating Dermatitis Herpetiformis. Presented by DR. MAURICE J. COSTELLO.

Anthony C. Cipollaro, M.D., *Chairman*

J. Lowry Miller, M.D., *Secretary*

March 4, 1952

Disseminated Lupus Erythematosus with Leg Ulcers. Presented by DR. LESLIE P. BARKER.

L. S., a woman aged 30, was first seen at the Vanderbilt Clinic in October, 1951, complaining of pretibial ulcers of five months' duration. These first developed in 1944, after trauma sustained in a German concentration camp. They healed in four months and remained so until June, 1951. In 1948 a serologic test for syphilis gave a positive reaction, and the patient has since received four 10-day courses of penicillin, the last being six weeks before the first visit to the Clinic. The penicillin had no effect on the ulcers. There was a history of "typhus and pneumonia" in 1943, "rheumatic fever" in 1944, two early abortions in 1949, Raynaud's disease in 1950, and persistent sensitivity to sunlight. She denies having had primary or secondary syphilitic lesions.

In October, 1951, the patient presented bilateral irregularly shaped pretibial ulcerations. The lesion on the right leg measured 2 by 2.5 in. (5 by 6.4 cm.) and was roughly round, with an irregular border. The base was red and granular and covered by a dirty-gray exudate. Surrounding the ulcer was a deep-red erythematous zone, about 1 in. (2.5 cm.) wide, studded with many pinhead-sized, blood-crusted areas, resembling excoriations. A similar, but smaller, ulcer was present on the left leg. No other dermatologic signs were present at that time.

Serologic reactions for syphilis were weakly positive numerous times. The treponemal immobilization test was negative. Plasma proteins were 8.8 mg. per 100 cc., with 4.6 gm. of albumin and 4.2 gm. globulin, per 100 cc. The cephalin flocculation test gave a 2+ reaction. The erythrocyte sedimentation rate varied between 110 and 120 mm. in one hour. The blood cell count was 3,200,000 red cells, 9.8 gm. hemoglobin per 100 cc., and 9,000 white cells. Smears for L. E. cells, using the patient's serum and buffy coat, showed a few cells on two occasions. Roentgenograms of the bones showed no abnormality, but those of the esophagus gave suggestive evidence of scleroderma. Two biopsies showed only granulation tissue. Tests for cryoglobulins were negative.

The patient was admitted to the Presbyterian Hospital, and the ulcers were treated surgically with skin grafts, which eventually closed the ulcers. With the history and laboratory findings, it was felt that a diagnosis of diffuse collagen disease could be entertained. While the patient was in the hospital, ill-defined red-purple patches were seen on the knuckles, and faint periungual telangiectases were seen on the fingers. She has been treated with benzazoline (priscoline®) hydrochloride, 200 mg. daily, for the past three months.

DISCUSSION

DR. MARION B. SULZBERGER: The patient was agitated and acted peculiarly; so I do not know whether one can rely on her history. But she repeatedly said her condition was worse in winter and on exposure to cold. On the record there is no notation that cryoglobulins were looked for. We have seen at the University Hospital a young woman with leg lesions that look somewhat like the lichenoid purpuric pigmented dermatosis of Gougerot and Blum, together with atypical purpuric lesions on the upper extremities and trunk, enlargement of the liver and spleen, and joint pains. In this case there is in the patient's serum a high titer of cryoglobulins, globulins in the gamma fraction, which precipitate out of the serum at room temperatures and go back into solution at higher temperatures. It would be well for us dermatologists in the future to bear in mind the possibility of cryoglobulins in studying patients with unexplained leg ulcers, with Raynaud's phenomenon, with acrocyanosis, acroasphyxia, sclerodactyly, polyarteritis, frostbite, lupus pernio, acral ulcerations, and other skin changes, perhaps including atypical lupus erythematosus and other dermatoses in which cold produces adverse effects.

DR. PAUL GROSS: Dr. Sulzberger's comments on cryoglobulin certainly are interesting. On the other hand, exposure to cold is not infrequently a precipitating factor in acute lupus erythematosus. Offhand, I can recall three cases in my own experience in which the onset of the disease could be traced to exposure.

DR. E. T. BERNSTEIN: Did the patient have fever? I don't know in which recognized category this case should fall. Certainly, it is not of the acute variety. The lupus erythematosus here should not be construed as something intrinsic or systemic in origin. The lupus erythematosus is coincident with large atrophies or ulcerations. She also has the feeling of a "dead" finger. In my estimation, the disease might be due to exposure to cold, but I can't see where the diagnosis of lupus erythematosus disseminatus enters in. What does the name mean, and why should climatic influences enter in?

DR. LESLIE P. BARKER: I admit this case has been rather confusing. The reason for a diagnosis of lupus erythematosus is that L. E. cells were found in the blood on two occasions. She has no skin lesions typical of lupus erythematosus except the erythematous telangiectasia on the dorsa of the tips of the fingers. The ulcers of the leg, I believe were traumatic. The test for cryoglobulins was negative. A diagnosis of cryoglobulin erythema was considered inconsistent.

Dermatomyositis. Presented by DR. PAUL GROSS.

I. U., a man aged 65, is presented from the Vanderbilt Clinic with an eruption on the scalp, face, chest, and hands, which appeared in May, 1950, accompanied by swelling of the eyelids. He was treated by two allergists and a dermatologist, but the condition did not respond. About April, 1951, he noticed weakness of the upper extremities, and about a month later, of the lower extremities also. He was admitted to the Neurological Institute in September, 1951, at which time he showed two types of cutaneous lesions. There were edema and erythema of the upper and lower eyelids and ill-defined purplish plaques on the dorsal aspects of the phalangeal and metacarpophalangeal joints of both hands. Larger erythematous areas, of mottled appearance, with erythema and telangiectases, were present on the shoulders, nuchal region, and chest. The other type of lesions consisted of psoriatic patches on the scalp, nasolabile folds, and midsternal region. There was pitting of the fingernails typical of psoriasis. The patient complained of extreme muscular weakness of the upper and lower extremities, and there was considerable wasting of the muscles of the pectoral girdle, hands, and right leg.

The erythrocyte sedimentation rate was 47 mm. in one hour; urinary creatine was 271 mg. per 100 cc., and creatinine, 774 gm. per 100 cc. X-ray examination revealed two areas of calcification near the cervical portion of the spine and one below the right clavicle.

Biopsy of the skin showed a somewhat atrophic, edematous epidermis, with slight hyperkeratosis and a fairly well-preserved, but thin, granular layer. In one of the sections there seemed to be some degeneration of the basal layer. The cutis was edematous in part, and finely fibrillar, with dilated superficial capillaries. A mild chronic inflammatory reaction was evident. There were also areas where the collagen appeared to be locally somewhat sclerotic, but most of the collagen bundles were widely separated. The morphology of the cutaneous lesions suggested poikiloderma, or perhaps even poikilosclerodermа. Sections of striated muscle tissue revealed fibers which were exceedingly eosinophilic and homogeneous. Some fibers were thin; others somewhat fragmented. There were, however, numerous muscle fibers where striae were easily seen. There were much edema in the tissue and areas of interstitial mononuclear infiltration. The diagnosis was degenerative myositis.

The patient received cortisone from Sept. 20 to Sept. 29, with resulting improvement of the cutaneous lesions but with no change in the muscular strength. He was discharged Oct. 4 and since then has been treated with nonsaponifiable fraction of wheat-germ oil (1 tsp. [4 cc.] three times a day). This, together with occupational therapy, has resulted in improvement. There has been no progression. The patient is able to dress himself, but the shoulders are "frozen," with abduction limited to about 30 degrees.

DISCUSSION

DR. BEATRICE M. KESTEN: This patient was in a hospital for nervous diseases for months before the skin lesions were thought of sufficient importance to justify calling in a dermatologist. All the symptoms are characteristic of dermatomyositis, at least to the dermatologist.

Pemphigus Vulgaris; Hyperadrenalism with Osteoporosis. Presented by DR. CARL T. NELSON.

E. M., a Jewish man aged 49, has previously been presented before this Section and before the New York Dermatological Society. He has suffered from pemphigus vulgaris of the skin and mucous membranes since 1948. Since 1949 he has been maintained on corticotropin or cortisone therapy, and since May, 1950, has shown evidences of hyperadrenalism in the form of increased pigmentation, moon facies, poikilodermatous changes in the skin, gynecomastia, elevated blood pressure, and a redistribution of body fat suggestive of the "buffalo-hump" type. The prompt reappearance of bullae upon cessation of corticosteroid therapy has necessitated the continuous administration of the hormones.

In May, after the patient had received 41,650 mg. of cortisone and 4,135 mg. of corticotropin, a roentgenogram of the lumbar portion of the spine revealed extensive demineralization of the vertebral column. Calcium and testosterone were then given in the hope of retarding the process. In June, 1951, the patient's pemphigus seemed to be escaping from cortisone control, and he was once more admitted for corticotropin therapy. Further roentgenographic studies revealed no change in the vertebral osteoporosis. A rather explosive outbreak of lesions while he was receiving corticotropin intramuscularly necessitated the simultaneous administration of cortisone and intravenous injections of corticotropin. Before the disease was finally brought under control, 22,325 mg. of cortisone and 1,100 mg. of corticotropin had been given, and 19,000 mg. of cortisone in addition was administered in the next three months on an ambulatory basis, with excellent control of the patient's blisters except for the lesions of the mouth. On Dec. 24, however, the patient suddenly complained of excruciating low back pain, with inability to stand or straighten his back. Roentgenograms now revealed multiple compression defects throughout the spine, as well as the previously noted osteoporosis.

At present the patient shows evidence of hyperadrenalism in the form of exophthalmos, increased pigmentation, areas of cutaneous atrophy, development of moon facies, humpback, and gynecomastia. No blisters are present, but their previous sites are marked by pigmentation. The mouth still shows numerous superficial erosions on the tongue and mucosa.

The complete blood cell count, urinary findings, and erythrocyte sedimentation rate were normal.

The cortisone dose has been reduced slowly, until he is now receiving 75 mg. daily. Estrogens and vitamin D have been added to testosterone for their calcium-deposition effect. Pain has slowly decreased and movement increased. A Tracy brace has been fitted in the orthopedic department. It is hoped that further reduction in the cortisone dose will be possible and that further osteoporosis will halt.

DISCUSSION

DR. DAVID BLOOM: This case demonstrates the value of corticotropin and cortisone therapy in pemphigus vulgaris. It also shows the resistance of the oral lesions to this treatment. Usually, however, the patients are able to take food without difficulty in spite of an incomplete response of the eruption of the mouth.

DR. CARL T. NELSON: This case was presented primarily to show one of the complications of corticosteroid therapy, namely, calcium loss and collapse of the lumbar vertebrae. The case emphasizes that these drugs must be used with caution. Through their ability to retard the formation of proteins from amino acids and to accelerate protein breakdown, the body stores of protein-bound calcium may be depleted. Calcium loss, particularly through the stool, but also through the kidney, may be sufficient to give the results seen in this case. The patient has received corticotropin or cortisone without let-up for over two years. We plan to continue this therapy as long as necessary to keep him in good condition. In the past, when the daily dose of cortisone has been below 100 mg., he has had acute exacerbations. At present there are no cutaneous manifestations, but the oral lesions persist. As Dr. Bloom mentioned, the latter are usually very slow to heal. Personally, I should like to stop cortisone treatment, but when one considers that this patient has been very ill in the past and that he has now been able to live a useful life with severe pemphigus for over four years, one is perhaps justified in trying to continue use of the hormones indefinitely, if necessary.

Behcet's Syndrome (Aphthosis): Relapsing Iritis with Resulting Blindness; Recurrent Genital and Oral Aphthae; Migrating Polyarthritis; Erythema Nodosum?; Involvement of the Central Nervous System; Nonspecific Reactivity of the Skin. Presented by DR. HELEN O. CURTH.

L. G., an Italian youth of 17, is presented from the Vanderbilt Clinic and the Neurological Institute. He had pleurisy (?) at 13 years of age. Two years ago, oral and genital ulcers appeared; these healed in about 10 days but recurred elsewhere. At one time a crater-like ulceration appeared on the right side of the scrotum, accompanied by inguinal adenopathy on the same side. Swelling of the right testis occurred several times. During the past year he has had discrete papular and pustular lesions on the lower part of the face and back, and occasionally there have been painful lumps on the back of the left leg. A year ago he had migrating polyarthritis, with high fever and considerable loss of weight, lasting several months. Seven months ago he complained of burning pain and inflammation of both eyes, with fogging of the vision and diplopia. After the last attack he could not see with either eye. In the summer of 1951, there developed tremor of the hands and difficulty in controlling his muscles; he walked like a drunken man and was excessively sleepy. With progression of the nervous disorder, mental deterioration has been observed. He received trihexyphenidyl (artane®) salicylates, aureomycin, cortisone, and chloramphenicol. He was admitted to the Presbyterian Hospital with a diagnosis of Johnson-Stevens disease or periarteritis nodosa. Later, the diagnosis was Behcet's syndrome. While the patient was in the hospital retinochoroiditis developed, with fibrinous exudate of the right eye. The lens was opaque, and the fundus was not visualized. The right pupil was fixed, and there were pupillary synechiae. There was active uveitis with a circumcorneal flush of the left eye, cloudiness of the cornea, and a muddy iris. The vitreous in the left eye was hazy but later cleared. The left optic disk, which at first could not be observed, was later hazy. He had nystagmus on lateral and upward gaze. He now has no light perception in the right eye and vision at a distance of 1 ft. (30 cm.) is limited to perception of hand movements in the left eye.

The patient was admitted to the Neurological Institute in January, 1952. He showed inconstant arm and leg movements, frequently giggled or laughed in euphoric manner, or was drowsy and lethargic. His speech was slurred and scanning. There were dysmetria and ataxia, more marked in the upper than in the lower extremities. Bilateral signs of cerebellar involvement were present. On admission he had bilateral third nerve paralysis, which subsided. Paresis of the right sixth nerve subsequently developed.

The patient has pinhead-sized pustular lesions on the inner aspect of the lips, sides of the tongue, soft palate, and buccal mucosa, some of which are surrounded by an inflammatory halo. At sites of intradermal skin tests with sterile saline solution or of venipunctures, small pustular lesions develop. There is paronychia of the left big toe.

Several months ago a soft aortic systolic murmur was heard. The liver was tender and enlarged by 1 to 2 fingerbreadths.

An electroencephalogram in September, 1951, showed diffusely abnormal changes. Lumbar punctures showed 115 cells per cubic millimeter, and this count later dropped to 15 and then to 2 cells per cubic millimeter. In February, 1952, the proteins of the spinal fluid, which had been 68 mg. per 100 cc., dropped to 25 mg. per 100 cc. Cultures from the scrotal lesion showed Bacillus subtilis, diphtheroids, Micrococcus pyogenes var. aureus, and Pseudomonas aeruginosa (Bacillus pyocyaneus). Tests for liver cell disease gave negative results, and a liver punch biopsy was normal. The erythrocyte sedimentation rate was 60 mm., later 41 mm., then 48 mm., and at present 5 mm., in one hour. An old-tuberculin test with a dilution of 1:100,000 produced an indurated papule 1 cm. in diameter, with surrounding erythema of 2.5 cm. Intradermal tests with sterile saline solution showed redness or pustules.

Biopsy of an ulcer of the scrotum was nondiagnostic.

A course of corticotropin therapy, 20 mg. in dextrose solution injected intravenously for 10 days, produced some improvement in the eyes, but this was not maintained. In general, the neurologic signs have remained stationary, except for minor changes in the extraocular movements. Inflammatory changes within the eyes have decreased, but vision has not improved. No arthritic changes have lately been noted. New oral lesions appear occasionally.

DISCUSSION

DR. PAUL GROSS: This case, in which there is such extensive involvement, including the cerebral tissue, would tempt one to reopen the question whether Behcet's disease is a clinical and etiologic entity which can be separated from aphthosis.

DR. HELEN O. CURTH: This is the fifth case in which involvement of the central nervous system has been reported. It is a serious manifestation, and some of the cases ended fatally. There is an additional case, not reported as one with involvement of the central nervous system, but terminating in a comatose state, which may have indicated some such involvement at the end. In these cases slurred speech, ataxia, and disturbances or weakness of movements are present. These, as well as other, manifestations of the syndrome may perhaps be explained by disturbances which begin as vascular lesions, most probably in the veins. This is the opinion of France, Buchanan, Wilson, and Sheldon (*Medicine* **30**:335, 1951), who collected 32 cases of Behcet's syndrome and added one of their own. In the case presented here there is involvement of the central nervous system in addition.

Sarcoid Occurring in a Tattoo. Presented by DR. CHARLES F. POST.

J. E. P., a Puerto Rican aged 30, is presented from the United States Public Health Service Hospital, Staten Island, N. Y., with a rash, of five months' duration, in the red areas of a tattoo on the left forearm. In 1941, in Washington, D. C., the patient had red and blue tattoos applied to the left and right forearms. In 1947 he sustained a fracture of the left radius, which was treated by means of a metal bone plate and four screws. There was good union of the fracture. In August, 1951, he noticed firm nodules in the red areas. They gradually increased in number and produced a weeping, crusting dermatitis. On Nov. 27, a tentative diagnosis of reaction to a galvanic current between the dye of the tattoo and the metal plate and screws was made. The plate was removed in December, 1951, and there has since been slow, but definite, improvement in the nodular eruption.

On the left forearm, there is an extensive tattoo, with a linear scar from the removal of the vitallium® plate extending the entire length on the side. In the central part of the tattoo, those red areas that overlie the plated portion of the radius exhibit a granulomatous dermatitis, with exudation and scaling. The blue areas are not involved, nor are the red areas away from the plated portion of the radius. A "conrol" tattoo applied at the same time on the right forearm is not involved in any manner.

Serologic tests for syphilis gave negative reactions. A scraping of the subcutaneous tissue in the region of one of the granulomatous lesions did not show acid-fast bacilli. Urinalysis and blood cell counts gave normal values. Blood chemistry studies showed 2.4 mg. of inorganic phosphorus per 100 cc., 3 Bodansky units of alkaline phosphatase, 11 mg. of calcium per 100 cc., and a total protein of 8.2 gm. per 100 cc., with 4.5 gm. of albumin and 3.7 gm. globulin, per 100 cc. Roentgenograms of the hands revealed no evidence of sarcoid; those of the chest showed questionable enlargement of the right hilar area, possibly consistent with the diagnosis of sarcoid. X-ray examination of the left radius and ulna after removal of the plate showed good union of the old fracture, but the screw holes remained unhealed. The tuberculin test gave a 2+ reaction.

Biopsy revealed that the epidermis was locally parakeratotic, edematous, and slightly infiltrated with leucocytes. In the cutis there were scattered cells which contained a black pigment, evidently the result of tattoo. There was also a granulomatous infiltration in the cutis. A granuloma which surrounded a hair follicle and penetrated deep into the specimen was composed of numerous epithelial tubercles composed of histiocytes, many of which contained pigment. A number of giant cells were present. A peripheral zone of lymphocytic infiltration was present. Pigment was also found in some of the giant cells. A smaller subepidermal epithelioid granuloma was noted, containing less pigment. Morphologically, the lesion resembled a sarcoid. The question arose as to whether the metallic plate had contained beryllium. Special staining failed to reveal any evidence of acid-fast bacilli. The diagnosis was sarcoidal granuloma and tattooing.

Metallurgical examination showed that the plate and screws were all of vitallium.® This has remained free of any electrolytic change. Vitallium® contains no trace of beryllium.

Without treatment other than removal of the plate, there has been gradual improvement of the eruption.

DISCUSSION

DR. MARION B. SULZBERGER: Possibly these pictures of sarcoid may be caused in some way by the metals of the plate. What is known about the alloys or metals in the vitallium® plate, the metal in the screws, etc.? Is there anything present known to be capable of causing a sarcoid reaction, such as beryllium, asbestos, or silica?

DR. CARL T. NELSON: Could the cinnabar possibly be beryllium-contaminated? I am not so much worried about the vitallium.®

DR. CHARLES F. POST: When the patient first appeared, I immediately conjectured that the case was one of a galvanic reaction between the metal bone plate and the mercury in the tattoo. Every one agreed, and about two days later the plate was removed from the bone. The patient has improved steadily since that time. This reaction is not due to cinnabar, because there is plenty of red tattoo elsewhere, and the reaction has occurred only over the plate. Cinnabar contains a little silicon, a trace of carbon, manganese, and molybdenum, but no beryllium. I have spoken with the laboratory that makes vitallium,® and they tell me it is not electrolytic or galvanic. Orthopedic men who introduced the use of vitallium® showed that if it is put in saline no rusting is apparent, as evidenced by rusty discoloration of the saline solution. However, if ordinary steel, for instance, is placed in saline solution along with vitallium,® the latter inhibits rusting of the steel. There must, therefore, be some ionization. I think we are left with the galvanism theory. Incidentally, I was able to find only one instance of sarcoid appearing in a tattoo area. This was a case of Michelson's reported by Madden in the late 1930's.

NOTE.—About two weeks after the patient was presented, he slipped on the steps of his home and fractured his radius at the site of the screw holes, where the plate had been removed. The arm was immediately placed in a cast again and is still in it (July 1, 1952). Two months after this second fracture the cast was removed and reapplied. At this time the nodular areas seen when he was presented had ulcerated, and the lesion looks much like lupus vulgaris.

Keratosis Follicularis with Intermittent Vesicular Eruption. Presented by DR. BEATRICE M. KESTEN.

A. D., a woman aged 48, is presented from the Vanderbilt Clinic with an eruption on the scalp, face, neck, upper part of the trunk, right arm, dorsum of the right hand, and inner aspect of the thighs. At the age of 15 she first noted an itching eruption on the face, which has slowly spread to the areas mentioned. During the winter many lesions disappear, leaving only pigmented spots. In the summer all lesions reappear and are extremely pruritic. In addition, the patient has had seven attacks of "herpes" on exposed and unexposed areas during the summer months. There is no familial history of similar disease.

At present there are a few discrete, yellowish-brown, small, oily papules scattered over the forehead, right side of the neck, and upper part of the trunk. In all the other areas mentioned there are numerous red or brownish macules. Along the right arm these macules are in bands. The patient has been observed for five years. During the summer months the typical papules occur in all the areas mentioned. In August, 1949, and September, 1951, the patient was seen with a grouped vesicular eruption on the face and neck and an erythematous papular eruption on the breast and extremities. The eruptions persisted about 10 days.

The urine was normal, with absence of porphyrin. A complete blood cell count and erythrocyte sedimentation rate were normal. The Mazzini reaction was negative. The basal metabolic rates were + 12 and + 4% on two occasions.

Biopsy revealed a localized invagination of the epidermis, filled with typical grains forming a loose plug, which surmounted an epidermal proliferation within the cutis. Within this proliferation were acantholysis and the formation of corps ronds. The lesion was surrounded by a cuticular inflammatory reaction. The changes noted are characteristic of keratosis follicularis. At the end of some of the sections were a few typical nevus cells, forming intraepidermal aggregates.

On tests for abnormal reaction to light (carbon-arc and Kromayer lamps), both the involved and the uninvolved areas of the skin (back, arm, and thigh) were about five times as sensitive to light as a normal skin of a subject of comparable age and color. The sensitivity lies within the sunburn spectrum. Erythema can be prevented by use of chemical sun screens.

Vitamin A, 100,000 units daily, has been administered for more than two years, without appreciable change in the eruption.

DISCUSSION

DR. DAVID BLOOM: This patient, as well as the patient with keratosis follicularis presented by Dr. Post, shows characteristic lesions of the mouth.

DR. PAUL GROSS: At least in this case, Dr. Kesten has demonstrated a true light sensitivity in keratosis follicularis (Darier's disease). I have always considered the development of new lesions after exposure to the sun, in keratosis follicularis, as well as in pityriasis rubra pilaris and pellagra, as a true Koebner phenomenon.

DR. BEATRICE M. KESTEN: The case was presented for three reasons: first, intermittent vesiculation brings up the question of the dry and wet forms of keratosis follicularis. Does this patient have what is known as chronic benign pemphigus? Second, as this patient has shown, there is sensitivity to the sunburn spectrum, which can be prevented by sun screens; third, after two years of vitamin A therapy there has been no improvement in the lesions.

Lupus Erythematosus with Squamous-Cell Epithelioma of the Ear. Presented by DR. DABNEY MOON-ADAMS.
Lupus Erythematosus with Poikiloderma-like Changes. Presented by DR. LEO SCHWEICH.
Chronic Disseminated Discoid Lupus Erythematosus with Poikiloderma-like Changes. Presented by DR. LEO SCHWEICH.
Keratosis Follicularis with Oral Lesions. Presented by DR. CHARLES F. POST.
Ichthyosis Hystrix. Presented by DR. HELEN O. CURTH.
Ichthyosis Hystrix with Features of Congenital Ichthyosiform Erythroderma (?) in Brother of Preceding Patient. Presented by DR. HELEN O. CURTH.
Leprosy, Mixed Type, with Lepromatous Reaction. Presented by DR. J. LOWRY MILLER.
Fox-Fordyce Disease. Presented by DR. F. PHILIP LOWENFISH.
Sicklemia with Ulcers of the Leg. Presented by DR. LEO SCHWEICH.
Vogt-Koyanagi Syndrome (?). Presented by DR. LESLIE P. BARKER.

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Jan. 18, 1952

Pemphigus Vulgaris (Vegetans). Presented by DR. M. H. SAMITZ and (by invitation) DR. M. S. GREENBERG, DR. J. COLETTI, and DR. J. GERMAN.

R. D., a white man aged 57, about March 1, 1951, noted lesions first on the buccal mucous membranes and later on the tongue and on the roof of the mouth. In July, 1951, an eruption appeared on the shoulders, which progressed to involve the arms, legs, trunk, and face.

In August, 1951, the mouth was the site of many large, eroded, macerated lesions and the lips were swollen and eroded. On the trunk, arms, legs, and face many bullae and eroded lesions were present. A vegetative crusted lesion was found on the right arm.

Urinalyses gave essentially normal results. Blood cell counts showed erythrocytes ranging from 3,700,000 to 5,640,000 and leucocytes from 9,200 to 12,700. The eosinophile chamber counts were 313 and 231 per cubic millimeter. The total proteins ranged from 6.0 to 6.48 mg.; albumin, from 2.99 to 3.98 mg.; globulin, from 2.48 to 3.01 mg., and serum sodium, from 296 to 315 mg., per 100 cc. The serum potassium was 22.5 mg. per 100 cc. The serologic tests for syphilis were negative.

The report on the biopsy specimen (Dr. H. Beerman) was as follows: "These sections revealed moderate hyperkeratosis with marked acanthosis, epithelial hyperplasia, and horny cysts. In some areas the hyperplasia was pseudoepitheliomatous. There were areas of denuded skin in which small groups of epithelial cells had lost their prickles and had become rounded. In several areas the papillae were apparently cut in cross section and were lined with two or three layers of these abnormal cells, resembling a trichoepithelioma."

The patient was treated with corticotropin (ACTH) initially. Later cortisone was substituted in a dose of 125 mg. a day. With improvement this was reduced to 50 mg. a day. X-ray therapy was used on the vegetative lesions.

DISCUSSION

DR. IRA L. SCHAMBERG: I have always thought of pemphigus as having a predilection for the axillary and crural regions. This patient, however, has no active lesions at these sites.

DR. LOUIS GOLDSTEIN: Many vegetating lesions are the result of secondary infection. It seems to me that penicillin might be indicated here.

DR. M. H. SAMITZ: The vulgaris picture was well controlled with cortisone, but there remained vegetative lesions about the mouth. These improved about 70% after x-ray and podophyllum treatment.

DR. HERMAN BEERMAN: The histologic sections showed a proliferation of the hair structures, in addition to the more superficial pemphigus-like picture. I wonder whether the original idea that this might be a combination of pemphigus and superficial epitheliomatosis may not be correct?

DR. FRED D. WEIDMAN: I think Dr. Goldstein's point is well taken. In the histologic sections of vegetative lesions there is usually a considerable leucocytic infiltration, a pronounced evidence of secondary infection. The picture does resemble somewhat a cancerous proliferation. Dr. Beerman and others will recall the case presented by Dr. Lever at the Academy meeting in Chicago; in the sections of that case it was difficult, indeed, to detect the tiny foci of degenerated squamous (order of Tzanck) cells. I mention this to indicate the extent to which the epithelial hyperplasia takes place, which should not be confused with a neoplastic proliferation. It is possible in these cases of the vegetative type by close scrutiny to recognize the features of genuine pemphigus. In other words, pemphigus vegetans is simply a variety of what Lever calls pemphigus maligna.

DR. ALBERT M. KLIGMAN: One should consider the possibility of superinfection with Candida.

Hydroa Vacciniforme (Bazin). Presented by DR. DOUGLASS A. DECKER, Allentown.

R. S., a white woman aged 63, presents some thickening of the skin on the exposed parts of the head, neck, arms, and hands. There are many vacciniform scars, varying in size from that of a pinhead to that of a dime, and loss of hair on the scalp.

In 1944, while at the seashore, the patient experienced "sun poisoning." Since then blisters have appeared on the exposed portions of her body after exposure to the sun. During some of these attacks, the patient has noticed red-colored urine. The present attack started on Aug. 13, 1951. After two weeks the patient went into coma and became incontinent. This condition cleared without medication in a few days. The blisters healed in five weeks.

Blood studies were reported as follows: Sept. 5, 1951: 84% hemoglobin; 3,800,000 erythrocytes and 18,150 leucocytes, with 77% polymorphonuclear leucocytes and 23% lymphocytes. Sept. 19: 84% hemoglobin; 4,100,000 erythrocytes and 9,250 leucocytes, with 49% polymorphonuclear leucocytes, 40% lymphocytes, 6% eosinophiles, 1% basophiles, and 4% monocytes.

DISCUSSION

DR. DOUGLASS A. DECKER, Allentown: This patient at one time had syphilis and was treated adequately for it. Last summer, when she became unconscious and lost control of the bladder and bowels, I asked a neurologist to see her, and for the first time I learned that this happens to patients with porphyrin in the urine. I saw the urine myself after the attack was over, and it was a brick-red color. The skin looks almost sclerodermatous, a result, I believe of the scarring.

DR. M. H. SAMITZ: I still think that lupus erythematosus of a systemic variety should be eliminated.

DR. DOUGLASS A. DECKER, Allentown: That never entered my mind. This woman had six or seven acute episodes and recovered spontaneously.

DR. BERTRAM SHAFFER: I think the proper diagnosis should be acute porphyria rather than hydroa vacciniforme. The latter, as Dr. Decker indicated, usually begins early in life and is not, as a rule, associated with systemic manifestations. The acute crises beginning in the adult and accompanied by neurologic and cerebral symptoms with dusky-red urine are found in acute porphyria.

DR. FRED D. WEIDMAN: This is indeed a remarkable case. I have never seen so extensive an involvement or one with such extreme thickening of the skin; just from inspection I should

never have thought for a moment of this diagnosis. Of course, with the history, it appears to be what Dr. Decker has stated. I think the first impression would be lupus erythematosus. It should be recalled that blebs can occur in pemphigus erythematodes, and one should never forget this possibility in all cases in which there is an apparent lupus erythematosus or seborrheiform dermatitis with blebs. Incidentally, occasionally the urine can become pink as a result of the saprophytic growth of certain pink yeast organisms, members of the Cryptococcideae (Torulopsidae), which one often sees growing on cultures from ringworm of the toes. The pink discoloration has been confused with hematuria.

Occupational Leucoderma from Rubber Apron and Also at Site of Garter. Presented by Dr. Joseph V. Klauder and Dr. Benjamin A. Gross.

Tuberculosis (Lupus Miliaris Faciei Disseminata). Presented by Dr. M. H. Samitz and (by invitation) Dr. J. Coletti.

Parapsoriasis (Plaque Type). Presented by Dr. Louis Goldstein.

Parapsoriasis Lichenoides. Presented by Dr. M. H. Samitz and (by invitation) Dr. M. S. Greenberg, Dr. J. Coletti, and Dr. J. German.

Parapsoriasis (Mucha-Habermann Type). Presented by Dr. M. H. Samitz and (by invitation) Dr. J. Coletti and Dr. J. German.

Weber-Christian Disease (Relapsing Febrile Nodular Nonsuppurative Panniculitis): First Case in the Negro. Presented by Dr. M. H. Samitz and (by invitation) Dr. J. Coletti and Dr. J. German.

Erythema Nodosum; Erythema Induratum; Weber-Christian Disease, Atypical. Presented by Dr. M. H. Samitz and (by invitation) Dr. J. Coletti and Dr. J. German.

Multiple Benign Sarcoid. Presented by Dr. M. H. Samitz and (by invitation) Dr. J. Coletti and Dr. J. German.

Case for Diagnosis: Majocchi's Disease (Purpura Annularis Telangiectodes) or Purpura Simplex (Nonthrombocytopenic Purpura)? Presented by Commander Bernard Geuting (MC), U. S. N.

Case for Diagnosis: Hansen-like Tuberculid? Presented by Dr. John P. Scully, Reading.

Cutis Verticis Gyrata, Probably Congenital. Presented by Dr. M. H. Samitz and (by invitation) Dr. J. Coletti.

Hemiatrophy of the Face with Telangiectasia. Presented by Dr. M. H. Samitz and (by invitation) Dr. J. Coletti and Dr. J. German.

Hypercholesteremia; Xanthoma Tuberosum (Tendon-Sheath Xanthoma). Presented by Dr. M. H. Samitz and (by invitation) Dr. J. Coletti and Dr. J. German.

Dermatitis Medicamentosa (Antipyrine) After Taking "666 Cold Preparation." Presented by Dr. Bernard L. Kahn.

Hemangioendothelioma, Resolving. Presented by Dr. M. H. Samitz and (by invitation) Dr. M. S. Greenberg, Dr. J. Coletti and Dr. J. German.

Familial or Hereditary Hemorrhagic Telangiectasia (Rendu-Osler-Weber Syndrome). Presented by Dr. M. H. Samitz and (by invitation) Dr. J. Coletti and Dr. J. German.

Tuberculosis (Papulonecrotic). Presented by Dr. M. H. Samitz and (by invitation) Dr. M. S. Greenberg.

Lupus Erythematosus? Vaselinoderma? Presented by Dr. M. H. Samitz and (by invitation) Dr. J. Coletti and Dr. J. German.

Fox-Fordyce Disease. Presented by Dr. Bernard L. Kahn.

Interesting Features of a Case of Congenital Syphilis. Presented by Dr. Joseph V. Klauder and Dr. Norman R. Ingraham Jr.

News and Comment

ANNOUNCEMENTS

Earl D. Osborne Fellowship in Dermal Pathology.—This fellowship, sponsored by the American Academy of Dermatology and Syphilology, is to provide annually for one year the opportunity for study and training in dermal pathology to a postgraduate student who has completed satisfactorily at least two years of training in dermatology or one of its allied branches in accordance with the requirements of the American Board of Dermatology and Syphilology. A stipend of $2,000 will be given to the candidate selected. The period of training will be spent at the Armed Forces Institute of Pathology, Washington, D. C., the appointment being subject to approval by the Director of the Institute. Since the American Board of Dermatology and Syphilology has approved the Institute for one year of training, the time spent will be accredited by the Board. The primary purpose of this fellowship is to train dermal pathologists. The large amount of material in dermal pathology at the Institute will be available for study, and, in special circumstances and with approval, original research may be undertaken under the direction of the chief of the dermal pathology section of the Institute.

Dermatologists in training who are interested may obtain application blanks for the Earl D. Osborne Fellowship from Dr. Hamilton Montgomery, Chairman of the Committee on Pathology of the American Academy of Dermatology and Syphilology, 102-110 Second Ave., S.W., Rochester, Minn. The next appointment available begins July 1, 1953.

Meeting of the Section on Dermatology of the American Medical Association.—At the next meeting of the Section on Dermatology of the American Medical Association to be held in New York City, June 1 through 5, 1953, a symposium will be presented on the subject of "Cutaneous Malignancies Embracing both Diagnosis and Treatment." Papers representing original work hitherto unpublished are earnestly solicited for this program. In addition, the usual variety of papers is also solicited at this time. Those wishing to appear on this program should contact Dr. J. Walter Wilson, Secretary, 3875 Wilshire Blvd., Los Angeles 5, Calif. as soon as possible, giving a brief résumé of the material.

Laboratory Training Courses.—The schedule of laboratory training Courses to be given by the Communicable Disease Center, January to December, 1953, is as follows:

Dates	Course No.	Courses	Duration	Location *
Jan. 5-9	9.40	Laboratory Diagnostic Methods in Veterinary Mycology	1 wk.	1
Jan. 12-23	8.72	Serology of Syphilis †	2 wk.	3
Jan. 26 to Feb. 6	8.40	Laboratory Diagnosis of Bacterial Diseases Part 1. General Bacteriology	2 wk.	2
Jan. 26 to Feb. 20	8.00	Laboratory Diagnosis of Parasitic Diseases Part 1. Intestinal Parasites	4 wk.	1
Feb. 2-13	8.72	Serology of Syphilis †	2 wk.	3
Feb. 9-20	8.41	Laboratory Diagnosis of Bacterial Diseases Part 2. General Bacteriology	2 wk.	2
Feb. 24 to March 6	8.50	Laboratory Diagnosis of Bacterial Diseases Enteric Bacteriology	2 wk.	2
Feb. 24 to March 13	8.01	Laboratory Diagnosis of Parasitic Diseases Part 2. Blood Parasites	3 wk.	1
March 9-20	8.72	Serology of Syphilis †	2 wk.	3
March 16-27	8.20	Laboratory Diagnosis of Virus Diseases ‡	2 wk.	5
March 16-27	9.37	Laboratory Diagnosis of Virus Diseases ‡§	2 wk.	5
March 16-27	8.15	Laboratory Methods in Medical Mycology Part 1. Cutaneous Fungi	2 wk.	1
March 16-27	8.55	Laboratory Diagnosis of Tuberculosis	2 wk.	2
March 30 to April 3	9.36	Laboratory Diagnosis of Tuberculosis §	1 wk.	2
March 30 to April 10	8.16	Laboratory Methods in Medical Mycology Part 2. Subcutaneous and Systemic Fungi ‖	2 wk.	1

Table Continued on Next Page

Dates	Course No.	Courses	Duration	Location *
April 6-10	9.34	Laboratory Diagnosis of Bacterial Diseases §	1 wk.	2
April 6-17	8.72	Serology of Syphilis †	2 wk.	3
April 13-17	9.33	Laboratory Diagnosis of Parasitic Diseases §	1 wk.	1
April 13-17	8.26	Laboratory Diagnosis of Rabies	1 wk.	2
April 27 to May 1	9.38	Laboratory Diagnosis of Venereal Diseases †§	1 wk.	4
May 4-8	9.60	Microbiology for Public Health Nurses	1 wk.	1
May 4-15	8.72	Serology of Syphilis †	2 wk.	3
May 18-29	8.74	Preparation and Standardization of Cardiolipin Antigens Used in Serologic Tests for Syphilis †	2 wk.	3
Aug. 17-28	8.72	Serology of Syphilis †	2 wk.	3
Sept. 14-25	8.72	Serology of Syphilis †	2 wk.	3
Sept. 21 to Oct. 2	8.40	Laboratory Diagnosis of Bacterial Diseases Part 1. General Bacteriology	2 wk.	2
Sept. 21 to Oct. 16	8.60	Laboratory Diagnosis of Parasitic Diseases Part 1. Intestinal Parasites	4 wk.	1
Oct. 5-16	8.41	Laboratory Diagnosis of Bacterial Diseases Part 2. General Bacteriology	2 wk.	2
Oct. 5-16	8.73	Preparation and Use of Controls in Serologic Tests for Syphilis †	2 wk.	3
Oct. 19-30	8.50	Laboratory Diagnosis of Bacterial Diseases Enteric Bacteriology	2 wk.	2
Oct. 19-30	8.20	Laboratory Diagnosis of Virus Diseases ‡	2 wk.	5
Oct. 19-30	9.37	Laboratory Diagnosis of Virus Diseases ‡§	2 wk.	5
Oct. 19 to Nov. 6	8.01	Laboratory Diagnosis of Parasitic Diseases Part 2. Blood Parasites	3 wk.	1
Oct. 26 to Nov. 6	8.72	Serology of Syphilis †	2 wk.	3
Nov. 2-6	9.34	Laboratory Diagnosis of Bacterial Diseases §	1 wk.	2
Nov. 9-13	9.36	Laboratory Diagnosis of Tuberculosis †	1 wk.	2
Nov. 9-13	8.26	Laboratory Diagnosis of Rabies	1 wk.	1
Nov. 9-20	8.74	Preparation and Standardization of Cardiolipin Antigens Used in Serologic Tests for Syphilis †	2 wk.	3
Nov. 16-20	9.33	Laboratory Diagnosis of Parasitic Diseases §	1 wk.	1
Nov. 16-27	8.55	Laboratory Diagnosis of Tuberculosis	2 wk.	2
Nov. 23-27	9.35	Laboratory Methods in Medical Mycology §	1 wk.	1
Nov. 30 to Dec. 11	8.17	Laboratory Methods in the Study of Pulmonary Mycoses	2 wk.	1
Dec. 7-18	8.72	Serology of Syphilis †	2 wk.	3
¶	8.05	Laboratory Diagnosis of Malaria	2 wk.	1
¶	8.10	Identification of Medically Important Arthropods	2 wk.	1
¶	8.21	Virus Isolation and Identification Techniques	2-4 wk.	5
¶	8.25	Laboratory Diagnosis of Influenza	1 wk.	5
¶	8.42	Typing of Corynebacterium diphtheriae	1 wk.	2
¶	8.51	Special Problems in Enteric Bacteriology	2 wk.	2
¶	8.52	Phage Typing of Salmonella typhosa	1 wk.	2
¶	8.75	Serologic Diagnosis of Rickettsial Diseases	1 wk.	2

* Location of Classrooms:
1 Bldg. 27, Chamblee, Ga.
2 Bldg. 30, Chamblee, Ga.
3 Bldg. 24, VDRL, Chamblee, Ga.
4 Bldg. 23, VDRL, Chamblee, Ga.
5 Virus Laboratory, Montgomery, Ala.

† Courses given by the Venereal Disease Research Laboratory, Division of Venereal Disease. Correspondence about these courses to be sent to Director, VDRL, P. O. Box 185, Chamblee, Ga.

‡ For this year, courses 8.20 and 9.37 have been combined.

§ These courses are designed for laboratory directors, senior laboratory staff members, physicians, and others of comparable professional standing.

‖ Completion of course 8.15 or equivalent education or experience is a prerequisite.

¶ Courses given by special arrangement only.

Information and application forms should be requested from Laboratory Training Services, Communicable Disease Center, U. S. Public Health Service, P. O. Box 185, Chamblee, Georgia.

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1. **Gaul, L. E., "Overtreatment Dermatitis", J.A.M.A., 127:439-442, 1945**
2. **Pillsbury, D. M., "Physiological Principles in the Management of Dermatitis", New Eng. J. Med., 244:423-429, 1951**
3. **Underwood, G. B. and Gaul, L. E., "Overtreatment Dermatitis of the Feet," J.A.M.A., 130:249-256, 1946**
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5. **Lane, C. G., "Therapeutic Dermatitis", New Eng. J. Med., 246:77-81, 1952**

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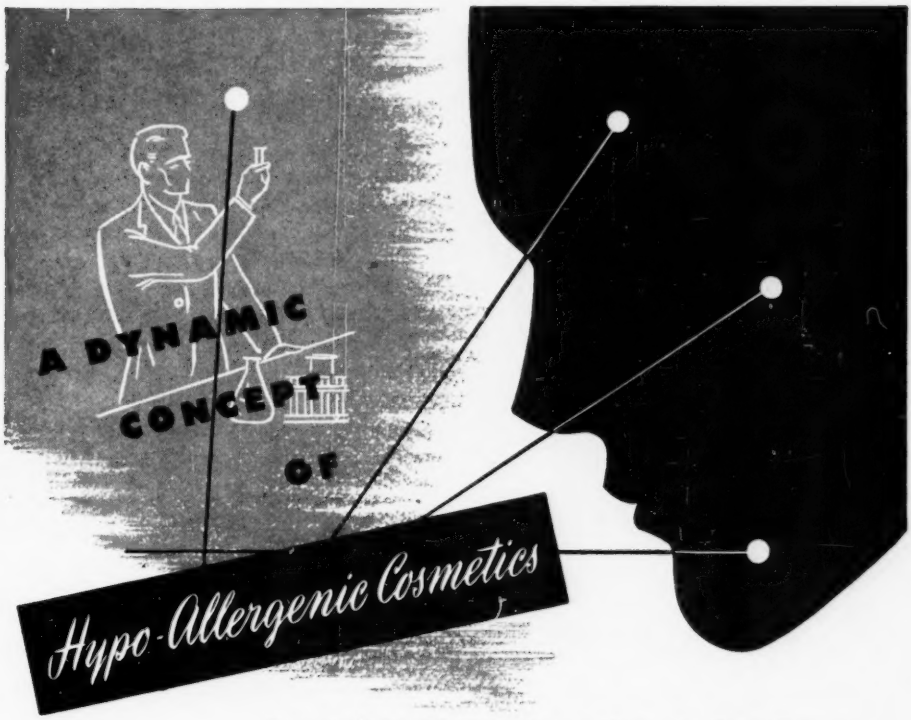

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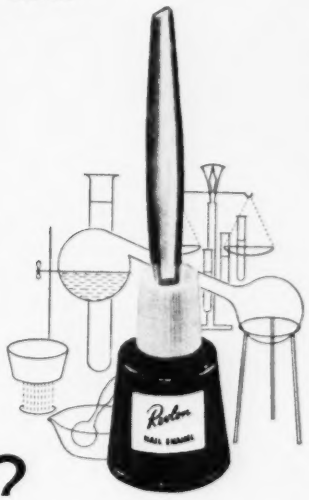

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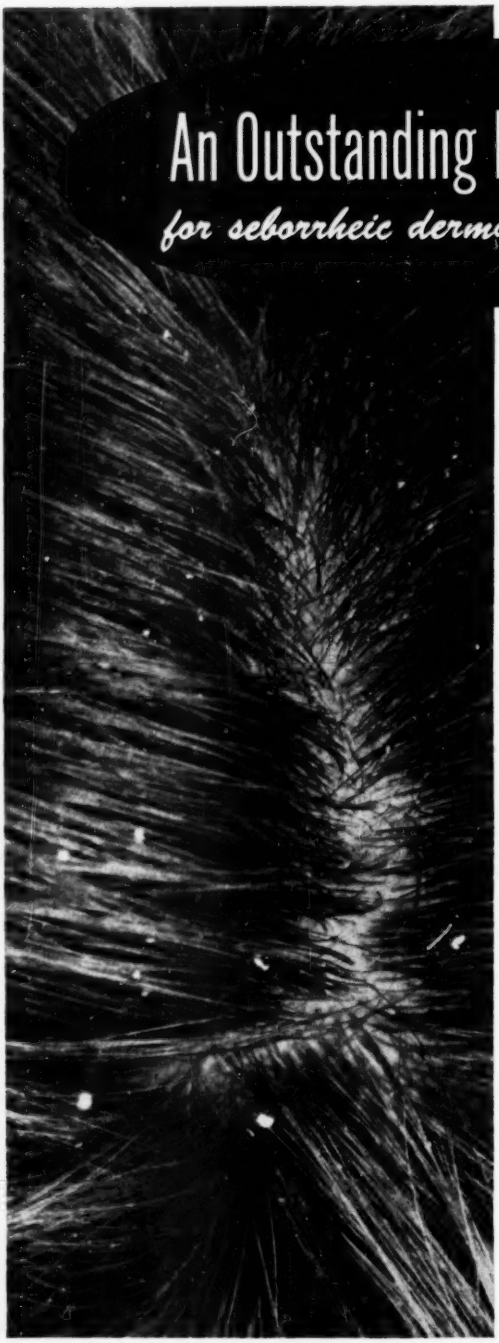

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1. Slinger, W. N., and Hubbard, D. M. (1951), Arch. Dermat. & Syph., 64:41, July.
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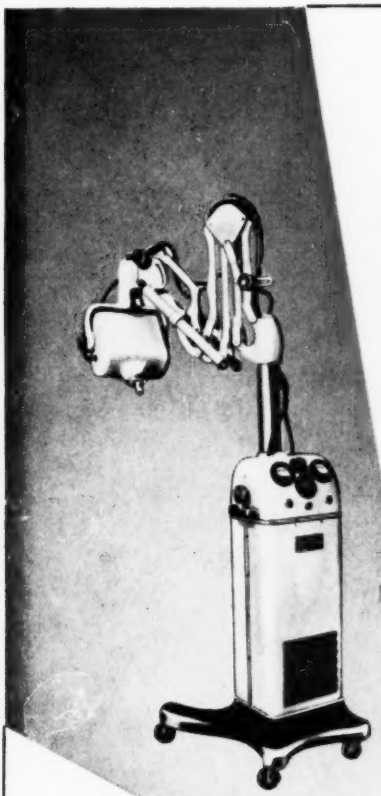

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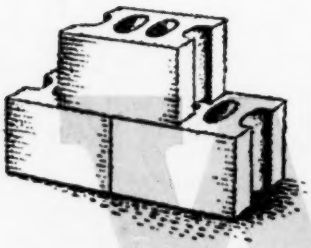

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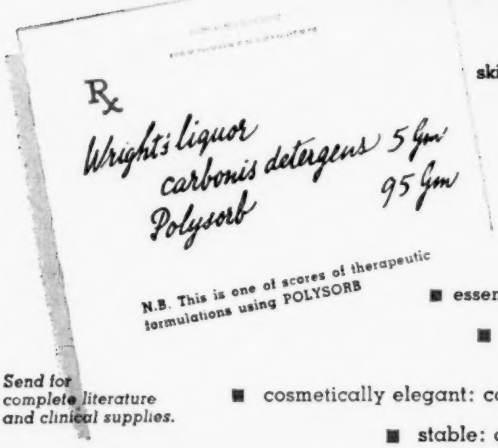
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